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EP-A- 0 184 162
EP-A- 0 227 355
EP-A- 0 323 042

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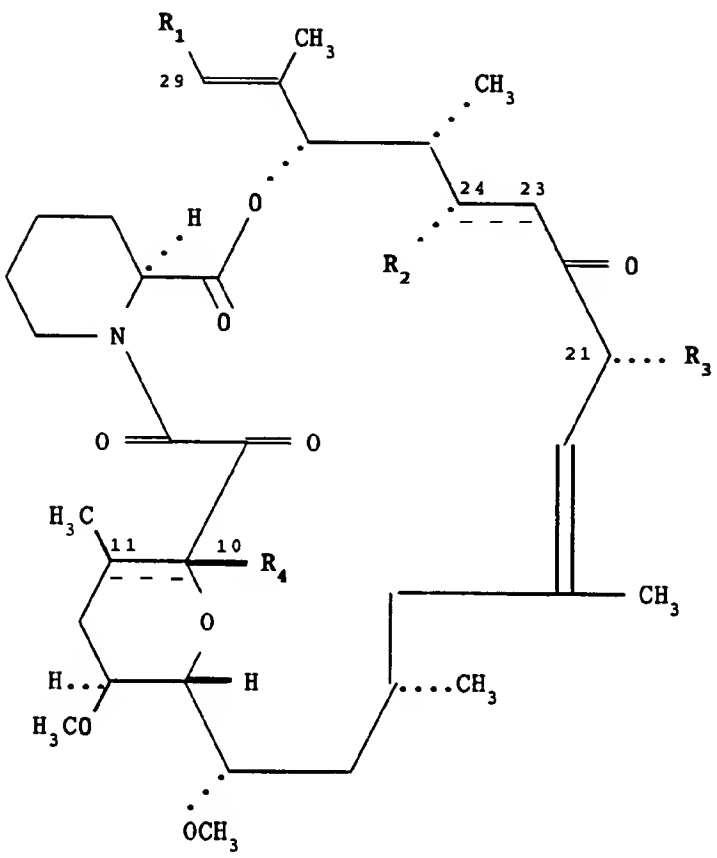
Description

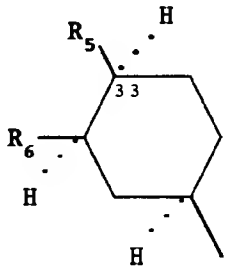
The invention relates to the field of macrolides. It concerns the compounds of formula I



I

wherein
either

R_1 is a group (a) of formula



(a)

wherein

R_5 is chloro, bromo, iodo or azido and

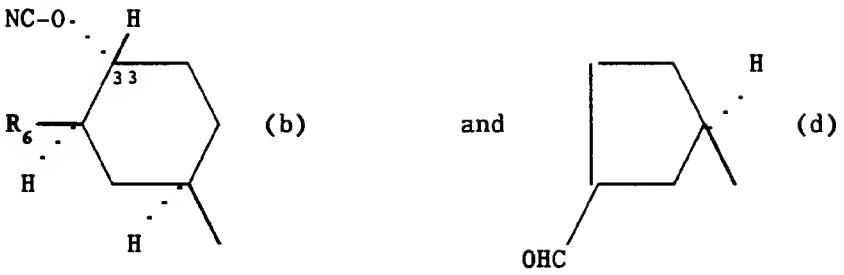
R_6 is hydroxy or methoxy;

R_2 is oxo and there is a single bond in 23,24 position; optionally protected hydroxy and there is a single or a double bond in 23,24 position; or absent and there is a double bond in 23,24 position; and

R_4 is hydroxy and there is a single bond in 10,11 position; or absent and there is a double bond in 10,11 position;

or

R_1 is a group (b) or (d) of formula



wherein

R_6 is as defined above;

R_2 is as defined above; and

R_4 is hydroxy and there is a single bond in 10,11 position; and

R_3 is methyl, ethyl, n-propyl or allyl;

in free form and, where such forms exist, in salt form,

hereinafter referred to as "the compounds of the invention".

As is evident from formula I and the definition of the substituents when there is a single bond in 10,11 position the carbon atom to which the methyl group in 11 position is attached has the β-configuration and there is a hydrogen atom with the α-configuration attached to the carbon atom in 11 position; when there is a double bond in 10,11 position this methyl group lies in the plane of the paper and there is no hydrogen atom in 11 position. When R_2 is oxo no hydrogen atom is attached to the carbon atom in 24 position.

R_1 preferably is a group (d). R_2 preferably is unprotected hydroxy and there is a single bond in 23,24 position. R_3 preferably is ethyl or allyl. R_4 preferably is hydroxy. R_5 preferably is chloro. R_6 preferably is methoxy.

Protected hydroxy preferably is hydroxy protected by a conventional hydroxy-protecting group such as formyl, tert-butoxycarbonyl, or trialkylsilyl; it especially is tert-butyldimethylsilyloxy.

A compound of the invention preferably is in free form. It preferably is in unprotected form.

A subgroup of compounds of the invention is the **compounds Ip$_1$**, i.e. the compounds of formula I wherein

R_1 is a group (a) wherein R_6 is methoxy and

either

R_5 is chloro or bromo and

R_4 is hydroxy and there is a single bond in 10,11 position

or

R_5 is azido and

R_4 is hydroxy and there is a single bond in 10,11 position or absent and there is a double bond in 10,11 position;

R_2 is optionally protected hydroxy and there is a single or a double bond in 23,24 position; and

R_3 is as defined above under formula I;

in free form and, where such forms exist, in salt form.

A further subgroup of compounds of the invention is the **compounds Ip$_3$**, i.e. the compounds of formula I wherein

R_1 is a group (b) wherein R_6 is methoxy,

R_2 is optionally protected hydroxy and there is a single bond in 23,24 position; or absent and there is a double bond in 23,24 position;

R_4 is hydroxy and there is a single bond in 10,11 position; and

R_3 is as defined above under formula I;

in free form and, where such forms exist, in salt form.

A further subgroup of compounds of the invention is the **compounds Ip$_4$**, i.e. the compounds of formula I wherein

R_1 is a group (d),

R_2 is optionally protected hydroxy and there is a single bond in 23,24 position; or absent and there is a double bond in 23,24 position;

R_4 is hydroxy and there is a single bond in 10,11 position; and

R_3 is as defined above under formula I;

in free form and, where such forms exist, in salt form.

A preferred subgroup of compounds of the invention is the compounds of formula I wherein

R_1 is a group (a) wherein R_5 is as defined above under formula I and R_6 is methoxy;

R_2 is optionally protected hydroxy and there is a single bond in 23,24 position;

R_4 is hydroxy and there is a single bond in 23,24 position; or absent and there is a double bond in 10,11 position; and

R_3 is ethyl or allyl.

A further preferred group of compounds of the invention is the compounds of formula I wherein

R_1 is a group (b) wherein R_6 is methoxy;

R_2 is optionally protected hydroxy and there is a single bond in 23,24 position; or absent and there is a double bond in 23,24 position;

R_4 is hydroxy and there is a single bond in 10,11 position; and

R_3 is ethyl or allyl.

A further preferred subgroup of compounds of the invention is the compounds of formula I wherein

R_1 is a group (d),

R_2 is optionally protected hydroxy and there is a single bond in 23,24 position; or absent and there is a double bond in 23,24 position;

R_4 is hydroxy and there is a single bond in 10,11 position; and

R_3 is ethyl or allyl.

A further subgroup of compounds of the invention is the **compounds Iq**, i.e. the compounds of formula I wherein

either

R_1 is a group (a) wherein R_5 is chloro, bromo, iodo or azido and R_6 is hydroxy or methoxy,

R_2 is oxo and there is a single bond in 23,24 position; optionally protected hydroxy and there is a single or a double bond in 23,24 position; or absent and there is a double bond in 23,24 position; and

R_4 is hydroxy and there is a single bond in 10,11 position; or absent and there is a double bond in 10,11 position;

or

R_1 is a group (b) or (d) wherein R_6 is hydroxy or methoxy;

R_2 is as defined above for this subgroup; and

R_4 is hydroxy and there is a single bond in 10,11 position; and

R_3 is methyl, ethyl, n-propyl or allyl,

in free form and, where such forms exist, in salt form.

A further subgroup of compounds of the invention is the **compounds Ir**, i.e. the compounds of formula I wherein

either

R_1 is a group (a) as defined above under formula I; and

R_2 and R_4 have the significance indicated above under group (a);

or

R_1 is a group (b) or (d) as defined above under formula I; and

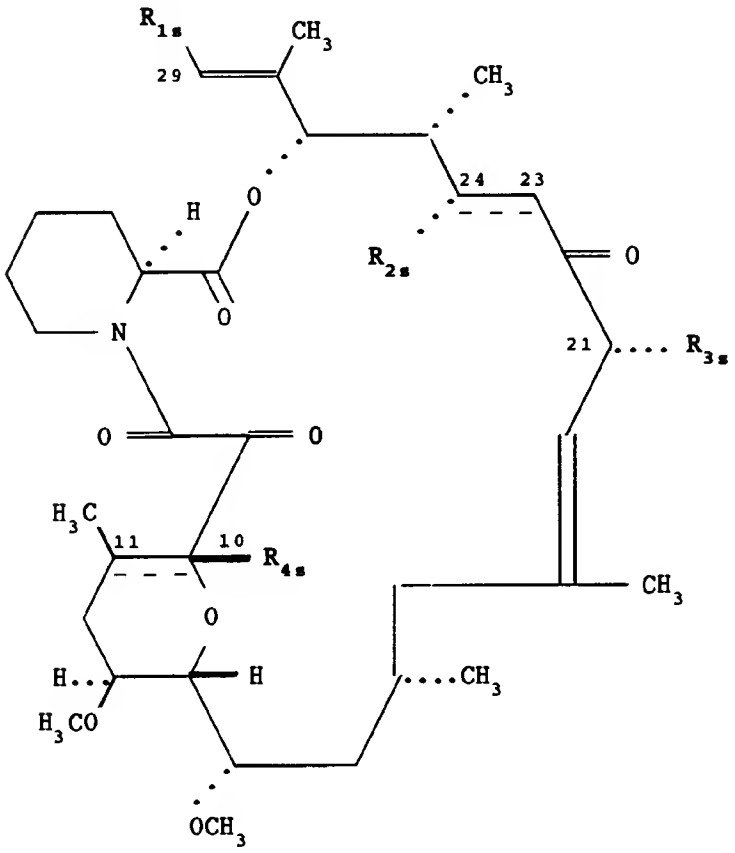
R_2 and R_4 have the significance indicated above under groups (b) and (d); and

R_3 is as defined above under formula I;

in free form and, where such forms exist, in salt form.

In a subgroup of compounds Ir R_2 is other than absent.

A further subgroup of compounds of the invention is the **compounds of formula Is**



Is

wherein
either

R_{1s} is a group (a) wherein R_5 is chloro, bromo, iodo or azido and R_6 is methoxy;

R_{2s} is hydroxy optionally protected by tert-butyldimethylsilyloxy and there is a single bond in 23,24 position; and

R_{4s} is hydroxy and there is a single bond in 10,11 position; or absent and there is a double bond in 10,11 position;

or

R_{1s} is a group (b) wherein R_6 is methoxy, or a group (d);

R_{2s} is hydroxy optionally protected by tert-butyldimethylsilyloxy and there is a single bond in 23,24 position; or absent and there is a double bond in 23,24 position; and

R_{4s} is hydroxy and there is a single bond in 10,11 position; and

R_{3s} is ethyl or allyl,

in free form and, where such forms exist, in salt form.

A compound of the invention can be obtained by a process comprising

a) for the preparation of a compound of formula I wherein

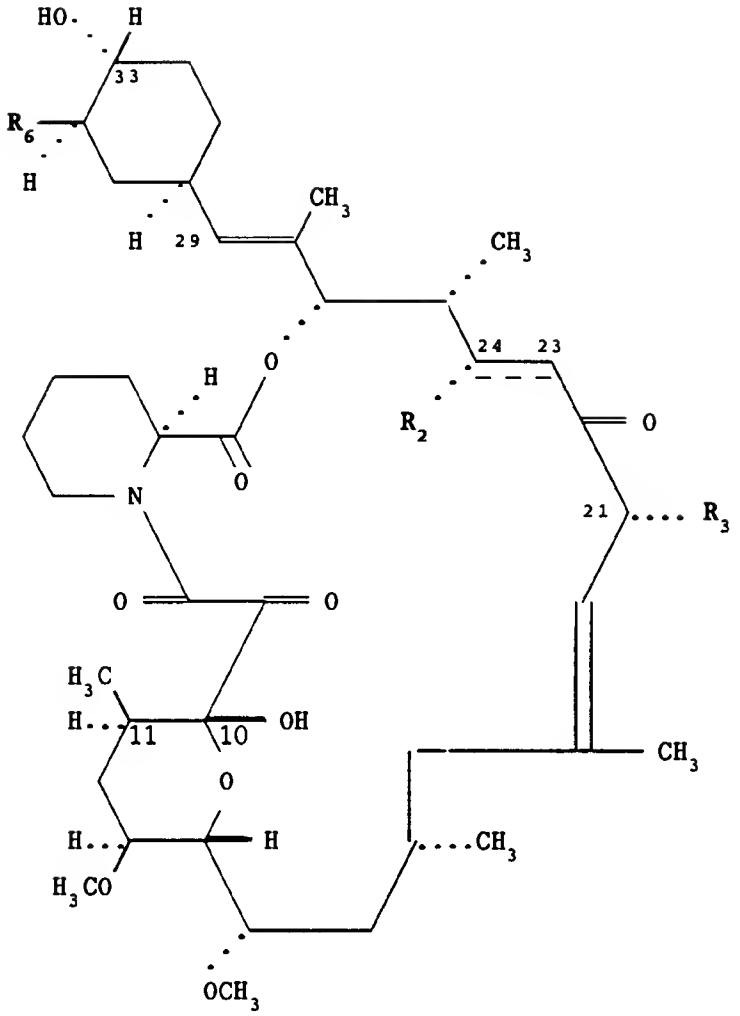
R_1 is a group (a) as defined above under formula I,

R_2 and R_3 are as defined above under formula I and

R_4 is hydroxy

(i.e. a **compound Ia**),

replacing under simultaneous epimerization the hydroxy group by chlorine, bromine, iodine or azido in a corresponding compound having unprotected hydroxy in 33 position (i.e. a **compound IIa**, of formula IIa



IIa

wherein R_2 and R_3 are as defined above under formula I and R_6 is hydroxy or methoxy);

b) for the preparation of a compound of formula I wherein

R_1 is a group (b) as defined above under formula I,

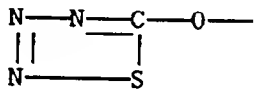
R_2 and R_3 are as defined above under formula I and

R_4 is hydroxy

(i.e. a **compound Ib**),

treating a corresponding compound IIa with cyanogen bromide in the presence of a base or

treating a corresponding compound IIa with thiophosgene, reacting the resultant product with an inorganic aside and allowing the resultant unstable intermediate having a group



in 33 position (i.e. a **compound IIb**) to decompose to a corresponding compound Ib;

c) for the preparation of a compound of formula I wherein

R_1 is a group (d) as defined above under formula I,

R_2 and R_3 are as defined above under formula I and

R_4 is hydroxy

(i.e. a **compound Ic**),

treating a corresponding compound Ib with an acid having a non-nucleophilic anion; and

- when a resultant compound of formula I has a protected hydroxy and/or a protected amino group,
  optionally splitting off the protecting group(s) to give a corresponding compound of formula I having one or more unprotected hydroxy and/or unprotected amino group(s)
  (i.e. a **compound Ij**),
  whereby when R_1 is a group (a), a water molecule may be simultaneously split off and a compound of formula I is obtained wherein
  R_1 is a group (a) as defined above under formula I,
  R_2 is unprotected hydroxy and there is a single or double bond in 23,24 position; and
  R_4 is absent and there is a double bond in 10,11 position
  (i.e. a **compound Ii**); or
- optionally protecting an unprotected hydroxy and/or unprotected amino group in a resultant compound of formula I as appropriate to give a corresponding compound of formula I having one or more protected hydroxy and/or protected amino groups(s) (i.e. a **compound Ik**),

and recovering the resultant compound of formula I in free form and, where such forms exist, in salt form.

The process variants of the invention can be effected in a manner analogous to known procedures.

Process variant a) is a substitution reaction under simultaneous epimerization. It is preferably effected in an inert solvent such as tetrahydrofurane or toluene. Preferably for the substitution by halogen the reaction is effected with tetrachloro-, tetrabromo- or tetraiodomethane in the presence of triphenylphosphine, and for the substitution by azido with azodicarboxylic acid ester, preferably diethyl ester, and hydrazoic acid. A hydroxy group in 24 position may be in protected form. As protecting group known hydroxy protecting groups such as tert-butyldimethylsilyl may be used. A protecting group may subsequently be split off in accordance with known procedures, e.g. with hydrofluoric acid in acetonitrile. Upon deprotection a water molecule may, depending on the reaction conditions chosen, simultaneously be split off in position 10,11 and a double bond formed. The individual compounds can be separated from such a resultant mixture in conventional manner, e.g. chromatographically.

Compounds Ia may be further processed by e.g. oxidation or dehydration to corresponding compounds wherein R_4 is absent; for example, oxidation of compounds Ia wherein R_2 is hydroxy leads to corresponding compounds wherein R_4 is absent and R_2 is oxo.

Process variant b) is a cyanidation reaction. It preferably is effected in an inert solvent such as a chlorinated hydrocarbon, e.g. dichloromethane. The temperature preferably is about room temperature. The base is e.g. 4-dimethylaminopyridine.

A compound of formula I obtained accordance to process variants a) and b) above may be isolated from the reaction mixture and purified in accordance with known methods. When R_2 is hydroxy and there is a single bond in 23,24 position a water molecule may be simultaneously split off. A corresponding mixture of compounds Ib is obtained wherein either R_2 is hydroxy and there is a single bond in 23,24 position or R_2 is absent and there is a double bond in 23,24 position. The individual compounds can be separated from such a resultant mixture in conventional manner, e.g. chromatographically.

The second procedure according to process variant b) is effected by reaction with thiophosgene, preferably in the presence of an acid scavenger such as 4-dimethylaminopyridine. Preferably an inert solvent such as acetonitrile is used. The temperature preferably is about room temperature. The subsequent reaction with an inorganic aside is preferably effected with sodium azide. The resultant compounds IIb are unstable and decompose already at room temperature to compounds Ib, under splitting off of nitrogen and sulfur. This reaction step preferably is effected in an inert solvent such as an aromatic hydrocarbon, e.g. benzene. Temperature preferably is elevated, e.g. about 50 °C.

In process variant c) a ring contraction takes place. Protecting groups which are present may be simultaneously split off. Preferably an inert solvent such as acetonitrile is used. Preferably hydrofluoric acid is used as acid having a non-nucleophilic anion. Temperature preferably is about room temperature.

The optional deprotection process variant may also be effect in conventional manner. For splitting off of e.g. tert-butyldimethylsilyl it is effected by treatment with e.g. hydrofluoric acid in a solvent such as acetonitrile. Depending on the reaction conditions selected (duration, temperature, etc.) the splitting can be steered in such a manner that either all or only some protecting group are removed. Partial deprotection is particularly indicated where a definite hydroxy group is to be subsequently reacted in a later reaction.

The optional protection step variant may also be effected in conventional manner along similar lines.

Thus for subsequent reactions involving a hydroxy group, particularly a hydroxy group in position 24 and/or 33, selective protection of only one of the two free hydroxy groups or selective deprotection of only one of the two protected hydroxy groups may be effected in such a manner that reaction occurs only at the desired position. Mixtures of end products may be obtained thereby; such mixtures can be separated in conventional manner, e.g chromatographically. Resultant end products still containing protecting groups can

be subsequently deprotected. Reaction conditions may alternatively be selected such that simultaneously with or immediately after reaction the protecting groups are removed (one pot process).

The compounds of formula I may be isolated and purified from the reaction mixture in conventional manner.

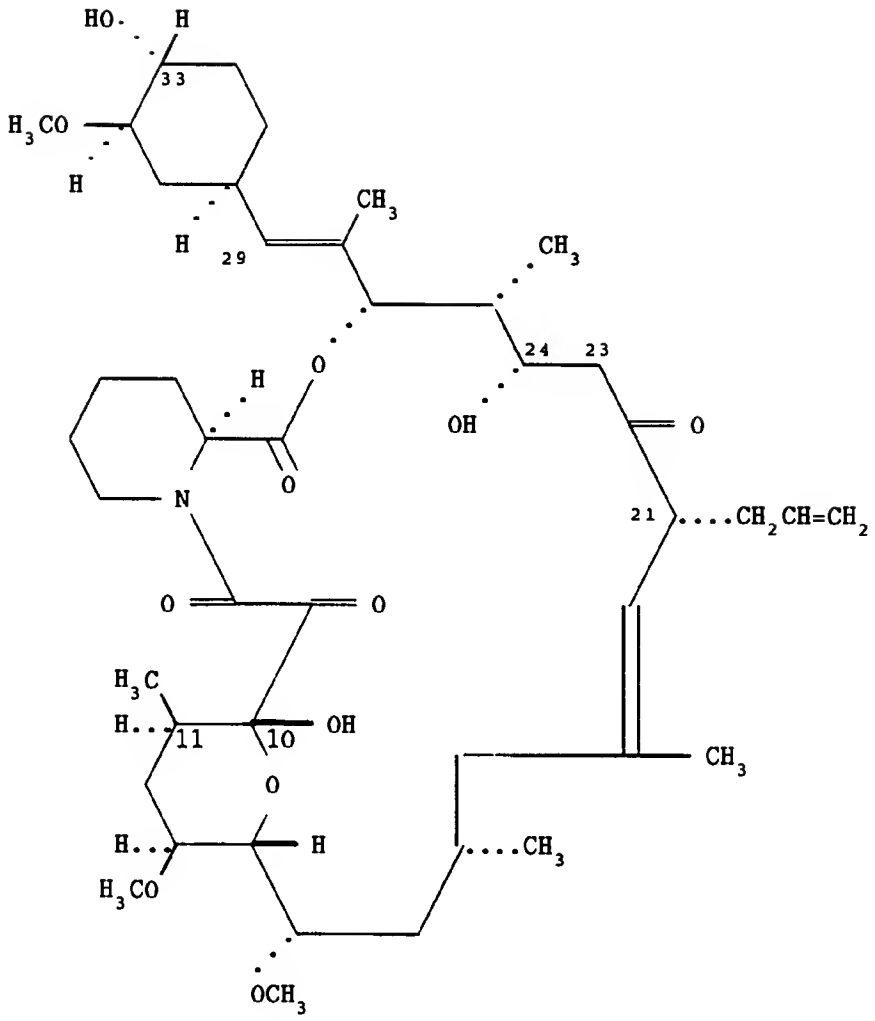
Insofar as their preparation is not specifically described herein, e.g. in the Examples, the compounds used as starting materials are known or can be obtained in conventional manner from known compounds, e.g. starting from appropriate Streptomyces strains such as Streptomyces tsukubaensis No. 9993 described in e.g. Fujisawa EP 184162. Samples can be obtained from the Fermentation Research Institute, Tsukuba, Ibaraki 305, Japan under provisions of the Budapest Treaty under deposit No. FERM BP-927. This strain has been redeposited on April 27, 1989 e.g. as disclosed in Sandoz EP 356399, with the Agricultural Research Culture Collection International Depository, Peoria, Illinois 61604, USA under the provisions of the Budapest Treaty under deposit No. NRRL 18488.

The following prior art has been cited during prosecution of the present filing:

- D1 = H.Tanaka et al., J.Am.Chem.Soc. 109 (1987) 5031-5033;
- D2 = Fujisawa EP-A-0 184 162;
- D3 = Fisons EP-A-0 323 042.

The following Examples illustrate the invention and are not limitative. All temperatures are in degrees Centigrade. All NMR spectra are in $CDCl_3$, ppm. The abbreviations have the following meanings:

BOC:	tert-butoxycarbonyl;
cfr:	colourless foamy resin:
db:	double bond;
Et:	ethyl;
FK 506:	the compound of formula



i.e. 17α-allyl-1β,14α-dihydroxy-12-[2'-(4''(R)-hydroxy-3''(R)-methoxycyclohex-1''(R)-yl)-1'-methyl-trans-vinyl]-23α,25β-dimethoxy-13α, 19,21α,27β-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-trans-ene-2,3,10,16-tetraone (according to the atom numbering in EP 184162; however, in the Examples the atom numbering of formula I is used throughout);

FR 520: as FK 506, but with ...CH_2CH_3 (ethyl) in place of allyl in position 21 in the formula;

iBuoyloxy: isobutanoyloxy [$(H_3C)_2CHCOO$-];

iPr: isopropyl;

na: not applicable;

N_3: azido;

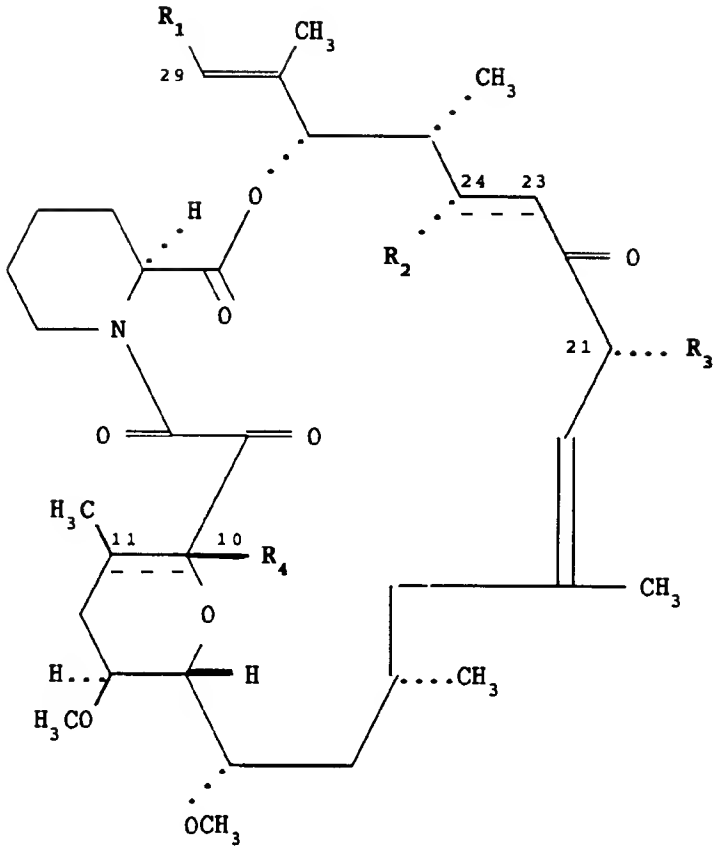
OMe (or MeO): methoxy;

OtBDMS: tert-butyldimethylsilyloxy;

sb: single bond;

tBu: tert-butyl.

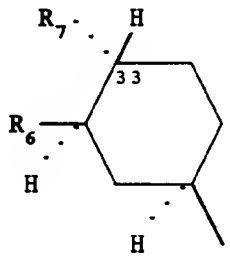
Examples 15 to 63 illustrate the preparation of compounds no longer encompassed by the scope of the present invention but useful as intermediates for the preparation of compounds of formula I. They are of formula X



X

wherein

R_1 is a group (c) of formula



(c)

wherein

R_6 is as defined above and

R_7 is oxo; optionally protected hydroxy; methoxy; methylthiomethoxy; isobutanoyloxy; aminooxalyloxy; R_8R_9CRCOO- wherein R_8 is optionally protected hydroxy or optionally protected amino and R_9 is hydrogen or methyl; or p-tolyloxythiocarbonyloxy;

R_2 is oxo and there is a single bond in 23,24 position; absent and there is a double bond in 23,24 position; or is optionally protected hydroxy, methoxy, methylthiomethoxy, isobutanoyloxy, aminooxalyloxy or R_8R_9CHCOO- wherein R_8 and R_9 are as defined above, and there is a single or a double bond in 23,24 position;

whereby for that group (c)

1) when R_7 is oxo, unprotected hydroxy or methoxy
then R_2 is other than absent and other than unprotected hydroxy or methoxy, and
there is a single bond in 23,24 position;

2) when R_6 is methoxy and R_7 is methylthiomethoxy
then R_2 is other than absent and other than unprotected hydroxy;
3) when R_6 is methoxy and R_7 is protected hydroxy
then R_2 is other than optionally protected hydroxy; and
4) when R_6 is hydroxy
then R_7 is other than optionally protected hydroxy; and

R_4 is hydroxy and there is a single bond in 10,11 position; and

R_3 is as defined above,

in free form and, where such forms exist, in salt form.

Example 1: 24-tert-Butyldimethylsilyloxy-33-epi-33-chloro-FK506

[Formula I: R_1 = a group (a) wherein R_5 = chloro, R_6 = OMe; R_2 = OtBDMS, single bond in 23,24 position; R_3 = allyl; R_4 = OH, single bond in 10,11 position]

[Process variant a), replacement with epimerization]

0.092 g **24-tert-butyldimethylsilyloxy-FK506** is heated for 15 hours under refluxing with 0.037 g triphenylphosphine in 4 ml of tetrachloromethane. The solvent is evaporated to dryness under reduced pressure and the residue is purified by column chromatography over silicagel using a mixture of hexane and acetic acid ethyl ester (2:1) as the eluant. The **title compound** is obtained (colourless foam):

^{1}H-NMR: about 2:3 mixture of conformers:
main conformer: 4.56 (m, $w_{1/2}$ = 7 Hz, H-33).

The starting material is obtained as follows:

a) 20 g **FK 506** is dissolved in 400 ml of dry dimethylformamide, 5.08 g imidazole and 11.25 g tert-butyldimethylchlorosilane is added in portions and the mixture is stirred for 110 hours at room temperature. The reaction mixture is diluted with acetic acid ethyl ester and washed five times with water. The organic phase is dried over sodium sulfate and the solvent distilled off under reduced pressure. The resultant crude product is purified by chromatography over silicagel using hexane/acetic acid ethyl ester 3:1 as the eluant. **24,33-Bis-(tert-butyldimehylsilyloxy)-FK 506** is obtained:

^{13}C-NMR: main conformer: 69.7 (C-24); 75.1 (C-33); 84.1 (C-32); 164.6 (C-8); 168.9 (C-1); 196.4 (C-9); 209.3 (C-22);
minor conformer: 70.9 (C-24); 75.3 (C-33); 84.1 (C-32); 165.8 (C-8); 168.2 (C-1); 191.2 (C-9); 210.0 (C-22);

b) 0.5 g 24,33-bis-(tert-butyldimethylsilyloxy)-FK506 is dissolved at 0° under stirring into a mixture of 10 ml of acetonitrile and 0.5 ml of 40 % hydrofluoric acid. After 2 hours at that temperature the reaction medium is diluted with dichloromethane. The solution is successively washed with saturated aqueous sodium bicarbonate solution and water and the organic phase is dried over sodium sulfate, and the solvent is evaporated under reduced pressure. The resultant residue is purified by column chromatography over silicagel (eluant: dichloromethane/methanol 9:1). **24-tert-Butyldimethylsilyloxy-FK 506** is obtained as a colourless foam:

^{13}C-NMR: main conformer: 69.7 (C-24); 73.6 (C-33); 84.1 (C-32); 164.6 (C-8); 168.9 (C-1); 196.4 (C-9); 209.2 (C-22);
minor conformer: 70.7 (C-24); 73.6 (C-33); 84.2 (C-32); 165.8 (C-8); 168.2 (C-1); 191.4 (C-9); 209.2 (C-22).

Example 2: 24-tert-Butyldimethylsilyloxy-33-epi-33-azido-FK506

[Formula I: R_1 = a group (a) wherein R_5 = azido, R_6 = OMe; R_2 = OtBDMS, single bond in 23,24 position; R_3 = allyl; R_4 = OH, single bond in 10,11 position]

[Process variant a)]

To a solution of 0.092 g **24-tert-butyldimethylsilyloxy-FK506** and 0.08 g triphenylphosphine in 2 ml of dry tetrahydrofurane is added at 0° 0.047 ml of azodicarboxylic acid diethyl ester, followed by 0.15 ml of a 2 M solution of hydrazoic acid in toluene. The solution is brought to room temperature and stirred for 18 hours. The solvent is evaporated to dryness under reduced pressure and the residue purified as described above under Example 1. The **title compound** is obtained (colourless foam):

The following compounds of formula I are obtained in analogous manner in accordance with process variant a):

Example No.	Analogous to Ex. No.	R_1	R_5	R_6	R_7	R_2	Position 23,24	R_3	R_4	Position 10,11	Physicochemical characterization data
3	1[1)]	(a)	Cl	OMe	na	OtBDMS	sb	Et	OH	sb	NMR*
4	1[1)]	(a)	Br	OMe	na	OtBDMS	sb	Et	OH	sb	
5	1[1)]	(a)	Br	OMe	na	OtBDMS	sb	allyl	OH	sb	
6	2[1)]	(a)	N_3	OMe	na	OtBDMS	sb	Et	OH	sb	
6a	1[1)]	(a)	I	OMe	na	OtBDMS	sb	Et	OH	sb	NMR*

*NMR: Example 3: ^{1}H-NMR: 4.56 (m, H-33);
Example 6a: ^{13}C-NMR: mixture of conformers: 210.33 (C-22); 168.91 (C-1); 164.59 (C-8); 123.64 (C-20); 78.90 (C-32); 25.81 (tBu).

[1)] The starting material is obtained from FR 520 in a manner analogous to 24-tert-butyldimethylsilyloxy-FK 506 (see Example 1):

a) **24,33-bis-(tert-butyldimethylsilyloxy)-FR 520:** ^{1}H-NMR: about 2:1 mixture of 2 conformers:
main conformer: 4.42 (m, H-2); 4.41 (db, 13 Hz, H-6 eq.); 4.05 (txt, J=1.5 Hz and 6 Hz, H-24); 3.80 (dxd, J=1.5 Hz and 10 Hz, H-14); 2.95 (dxdxd, J=4 Hz, 8 Hz and 11 Hz, H-32);
minor conformer: 4.25 (q, J=5 Hz, H-24); 3.94 (dxd, J=2 Hz and 10 Hz, H-14); 2.95 (dxdxd, J=4 Hz, 8 Hz and 11 Hz, H-32);

b) **24-tert-butyldimethylsilyloxy-FR 520:** ^{1}H-NMR: about 2:1 mixture of 2 conformers:
main conformer: 4.44 (b, H-2); 4.42 (db, J=13 Hz, H-6 eq.); 4.05 (dxt, J=1,5 Hz and 6 Hz, H-24); 3.81 (dxd, J=1.5 Hz and 10 Hz, H-14); 3.01 (dxdxd, J=4 Hz, 8 Hz and 11 Hz, H-32);
minor conformer: 4.24 (H-24); 3.94 (dxd, J=2 Hz and 10 Hz, H-14); 3.01 (dxdxd, J=4 Hz, 8 Hz and 11 Hz, H-32).

Example 7: 24-tert-Butyldimethylsilyloxy-33-cyanoxy-FR 520

[Formula I: R_1 = a group (b) wherein R_6 = OMe; R_2 = OtBDMS, single bond in 23,24 position; R_3 = Et; R_4 = OH, single bond in 10,11 position]

[Process variant b), treatment with cyanogen bromide]

A solution of 2 g **24-tert-butyldimethylsilyloxy-FR 520** and 0.94 g 4-dimethylaminopyridine in 100 ml of dichloromethane is rapidly reacted at room temperature with a solution of 0.4 g cyanogen bromide in 15 ml of dichloromethane and the mixture is stirred at room temperature for 20 minutes. The mixture is filtered over silicagel (eluant: n-hexane/acetic acid ethyl ester) and the solvent is removed from the relevant fraction under reduced pressure. The **title compound** is obtained as a colourless foamy resin:

^{1}H-NMR: mixture of conformers: 4.3 (m; H-33).

Example 8: 24-tert-Butyldimethylsilyloxy-33-cyanoxy-FR 520

[Formula I: as for Example 7]

[Process variant b), treatment with thiophosgene and sodium azide]

A solution of 2 g **24-tert-butyldimethylsilyloxy-FR 520** and 2 g 4-dimethylaminopyridine in 50 ml of acetonitrile is carefully reacted with 0.4 ml of thiophosgen and the mixture stirred for 3 hours at room temperature. The reaction mixture is poured onto a well-stirred mixture consisting of 150 ml of acetic acid ethyl ester, 40 ml of saturated aqueous sodium chloride solution and 50 ml of 2 N sodium azide solution, vigourous stirring is continued for 5 minutes and the organic phase is separated. The organic phase is then successively washed with water, 1 N hydrochloric acid solution, water, and saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue is taken up in about 100 ml of benzene and heated at 30-40° for 2 hours. The benzene is removed under reduced pressure and the **title compound** is recovered from the residue as a colourless foamy resin by column chromatography over silicagel (eluant: n-hexane / acetic acid ethyl ester):

^{1}H-NMR: see Example 7.

The following compounds of formula I are obtained in analogous manner in accordance with process variant b):

Example No.	Analogous to Ex. No.	R_1	R_5	R_6	R_7	R_2	Position 23,24	R_3	R_4	Position 10,11	Physicochemical characterization data
9	7,8	(b)	na	OMe	na	OtBDMS	sb	allyl	OH	sb	NMR*
10a[1)]	7,8	(b)	na	OMe	na	OH	sb	Et	OH	sb	NMR*
10b[1)]	7,8	(b)	na	OMe	na	absent	db	Et	OH	sb	NMR
11a[2)]	7,8	(b)	na	OMe	na	OH	sb	allyl	OH	sb	
11b[2)]	7,8	(b)	na	OMe	na	absent	db	allyl	OH	sb	

*NMR: Example 9: ^{1}H-NMR: mixture of conformers: 4.3 (m, H-33);

Example 10a: ^{1}H-NMR: mixture of conformers: 5.34 (H-26); 4.63 (db, J=4 Hz, H-2); 4.44 (db, J=13 Hz, H-6 eq.); 4.30 (dxdxd, J=5 Hz, 8 Hz and 11 Hz, H-33); 3.01 (tb, J=13 Hz, H-6ax.);

Example 10b: ^{1}H-NMR: 6.81 resp. 6.75 (dxd resp. dxd, J=5 Hz and 15 Hz resp. 7 Hz and 15 Hz, H-24); 6.2 resp. 6.3 (dxd resp. dxd, J=2 Hz and 15 Hz resp. 1 Hz and 15 Hz, H-23); 5.29 resp. 5.23 (d resp. d, J=3 Hz resp. 3 Hz, H-26); 4.3 (m, H-33);

1)2) A mixture of both compounds is obtained; they can be separated chromatographically (eluant: n-hexane/acetic acid ethyl ester).

Example 12: 29-Des-(4-hydroxy-3-methoxycyclohexyl)-29-(3-formylcyclopentyl)-FR 520

[Formula I: R_1 = a group (d); R_2 = OH, single bond in 23,24 position; R_3 = Et; R_4 = OH, single bond in 10,11 position]

[Process variant c), treatment with a non-nucleophilic anion]

0.5 g **24-tert-butyldimethylsilyloxy-33-cyanoxy-FK 520** (compound of Examples 7 and 8) or **33-cyanory-FR 520** (compound of Example 10a) is dissolved into a mixture of 50 ml of acetonitrile and 2 ml of 40 % wt. aqueous hydrofluoric acid and the mixture is stirred for 2.5 hours at room temperature. The reaction mixture is then distributed between acetic acid ethyl ester and saturated aqueous sodium bicarbonate solution, the aqueous phase is discarded and the organic phase is washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and concentrated under reduced pressure. The **title compound** is obtained as a colourless foamy resin from the residue by column chromatography over silicagel (eluant: n-hexane / acetic acid ethyl ester):

^{1}H-NMR: mixture of conformers: 9.64 (d, J=2 Hz, CHO); 2.87 (m, H-32); 2.67 (m, H-30).

The following compounds of formula I are obtained in analogous manner in accordance with process variant c):

Example No.	Analogous to Ex. No.	R_1	R_5	R_6	R_7	R_2	Position 23,24	R_3	R_4	Position 10,11	Physicochemical characterization data
13	12[1)]	(d)	na	na	na	OH	sb	allyl	OH	sb	NMR*
14	12[2)]	(d)	na	na	na	absent	db	Et	OH	sb	NMR*

*NMR: Example 13: ^{1}H-NMR: mixture of conformers: 9.65 (d, J=2 Hz, CHO); 2.86 (m, H-32); 2.15 (dxdxd, J=12.5 Hz and 7.5 Hz and 5 Hz, H-31a); 1.45 (dxt, J=12.5 and 9 Hz, H-31b); 2.67 (m, H-30);

Example 14: ^{1}H-NMR: about 5:3 mixture of conformers: 9.66 (d, J=2 Hz, CHO); 6.83 (dxd, J=15 and 5 Hz) resp. 6.77 (dxd, J=15 and 7.5 Hz) H-24; 6.19 (dxd, J=15 and 1.5 Hz) resp. 6.30 (dxd, J=15 and 1 Hz) H-23;

1) Starting from the compound of Example 9 or 11a;
2) Starting from the compound of Example 10b.

Example 15: a) 24-tert-Butyldimethylsilyloxy-33-oxo-FK506 and
b) **24-tert-Butyldimethylsilyloxy-33-methylthiomethoxy FK 506**

[Formula X: R_1 = a group (c) wherein R_5 = OMe, R_7 = oxo and, respectively, methylthiomethoxy; R_2 = OtBDMS, single bond in 23,24 position; R_3 = allyl; R_4 = OH, single bond in 10,11 position]

1 g **24-tert-Butyldimethylsilyloxy-FK 506** is dissolved at room temperature into a mixture of 20 ml of acetic anhydride and 30 ml of dimethylsulfoxide and stirring is effected for 5 hours at room temperature. The reaction mixture is poured onto a mixture of acetic acid ethyl ester and potassium carbonate solution, stirred for 20 minutes, the phases are separated and the organic phase is repeatedly washed with water, dried over sodium sulfate, filtered and concentrated under reduced pressure. Following column chromatographic fractionation of the residue over silicagel (eluant: acetic acid ethyl ester / n-hexane 2:1) the **title compounds** are obtained as colourless foamy resins.

The following compounds of formula X are obtained in analogous manner as colourless foamy resins:

Example No.	Analogous to Ex. No.	R_1	R_5	R_6	R_7	R_2	Position 23,24	R_3	R_4	Position 10,11
16a	15[1)]	(c)	na	OMe	OtBDMS	OCH_2SCH_3	sb	allyl	OH	sb
16b	15[1)]	(c)	na	OMe	OtBDMS	oxo	sb	allyl	OH	sb
16c	15[2)]	(c)	na	OMe	oxo	OtBDMS	sb	Et	OH	sb
16d	15[3)]	(c)	na	OMe	OtBDMS	oxo	sb	Et	OH	sb

1) Starting from 33-tert-butyldimethylsilyloxy-FK 506 (compound of Example 16 in EP 184162);
2) eluant: toluene / acetic acid ethyl ester 9:1;
3) Starting from 24-tert-butyldimethylsilyloxy-FR 520;
Starting from 33-tert-butyldimethylsilyloxy-FR 520 (DOS 39 38 754);

Example 17: 33-p-Tolyloxythiocarbonyloxy-FK506

[Formula X: R_1 = a group (c) wherein R_6 = OMe, R_7 = p-tolyloxythiocarbonyloxy; R_2 = OH, single bond in 23,24 position; R_3 = allyl; R_4 = OH, single bond in 10,11 position]

A solution of 2 g **FK 506** in 70 ml of acetonitrile is successively reacted with 0.46 g 4-dimethylaminopyridine and 1.8 g p-tolyloxythiocarbonyl chloride and the mixture is stirred for 15 hours at room temperature. The reaction mixture is then diluted with acetic acid ethyl ester and successively washed with saturated aqueous sodium bicarbonate solution, 0.5 N hydrochloric acid and water, dried over sodium sulfate, filtered and concentrated under reduced pressure. The **title compound** is isolated from the residue as a light yellow foamy resin by column chromatography over silicagel (eluant: acetic acid ethyl ester / n-hexane 1:1).

Example 18: 33-Aminomethylcarbonyloxy-Δ^{23} -FK506

[Formula X: R_1 = a group (c) wherein R_6 = OMe, R_7 = R_8R_9CHCOO-(R_8 = amino; R_9 = H); R_2 = absent, double bond in 23,24 position; R_3 = allyl; R_4 = OH, single bond in 10,11 position]

2 g N-BOC-glycine, 1 g dicyclohexylcarbodiimide, 0.5 g Δ^{23} **-FK 506** (second compound of Example 17 in EP 184162) and 1 g 4-dimethylaminopyridine are successively taken up at room temperature in 70 ml of acetonitrile and the mixture is stirred for 20 minutes at room temperature. The reaction mixture is filtered, the filtrate diluted with acetic acid ethyl ester and successively washed with 1 N hydrochloric acid, aqueous sodium bicarbonate solution and water, the organic phase is dried over sodium sulfate, filtered, concentrated, and the **residue** is taken up in 50 ml of acetonitrile.

In order to split off the protecting group 0.5 g p-toluenesulfonic acid monohydrate is added and the mixture heated to refluxing for 5 minutes, the solution is cooled off, diluted with acetic acid ethyl ester, washed to neutrality with water, the organic phase is dried over sodium sulfate and concentrated. From the residue the **title compound** is obtained as a colourless foamy resin after column chromatography over silicagel (eluant: acetic acid ethyl ester / methanol 20:3).

Example 19: 24-tert-Butyldimethylsilyloxy-FR 520-33-[(tert-butyldimethylsilyloxy)-(S)-lactate]

[Formula X: R_1 = a group (c) wherein R_6 = OMe, R_7 = R_8R_9CHCOO-(R_8 = OtBDMS, R_9 = Me, S-configuration); R_2 = OtBDMS, single bond in 23,24 position; R_3 = Et; R_4 = OH, single bond in 10,11 position]

To a solution of 450 mg **24-tert-butyldimethylsilyloxy-FR 520** and 120 mg tert-butyldimethylsilyloxy-(S)-lactic acid in 10 ml of dichloromethane are added at room temperature 120 mg N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride and 23 mg dimethylaminopyridine. After 60 hours the reaction mixture is diluted with acetic acid ethyl ester, washed successively with 0.5 N hydrochloric acid and then water, dried over sodium sulfate, filtered, and the solvent is evaporated under reduced pressure. The residue is chromatographed over silicagel (eluant: n-hexane / acetic acid ethyl ester 2:1). The **title compound** is obtained as a colourless foam.

Example 20: FK 506-33-glycolate

[Formula X: R_1 = a group (c) wherein R_6 = OMe, R_7 = R_8R_9CHCOO- (R_8 = OH, R_9 = H); R_2 = OH, single bond in 23,24 position; R_3 = allyl; R_4 = OH, single bond in 10,11 position]

To a solution of 300 mg tert-butyldimethylsilyloxymethylcarboxylic acid in 5 ml of dichloromethane are added under stirring at 0° 0.67 ml of oxalyl chloride and one drop of dimethylformamide. The mixture is brought to room temperature and is stirred for 1 hour. The reaction mixture is concentrated under reduced pressure. The residue is taken up in 5 ml of dichloromethane and this solution is added dropwise at 0° to a solution of 600 mg **FK 506,** 0.28 ml triethylamine and a catalytic quantity of 4-dimethylaminopyridine. After 18 hours stirring at 0° the solution is diluted with acetic acid ethyl ester, successively washed with 0.1 N hydrochloric acid and water, the organic phase is dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue is taken up in 20 ml of acetonitrile, reacted with 0.5 ml of 40 % wt. aqueous hydrofluoric acid and stirred for 20 minutes at room temperature. The mixture is diluted with acetic acid

ethyl ester, washed with saturated aqueous sodium hydrogen carbonate solution, dried over sodium sulfate, filtered and concentrated under reduced pressure. The **title compound** is obtained as a colourless foamy resin from the residue by chromatography over silicagel (eluant: n-hexane / acetic acid ethyl ester).

The following compounds of formula X are obtained in analogous manner as a colourless foamy resin:

Example No.	Analogous to Ex. No.	R_1	R_5	R_6	R_7	R_2	Position 23,24	R_3	R_4	Position 10,11
21	17 to 20	(c)	na	OMe	BOC-NHCH$_2$COO-	OtBDMS	sb	allyl	OH	sb
22	17 to 20	(c)	na	OMe	tBDMS-OCH$_2$COO-	OtBDMS	sb	allyl	OH	sb
23	17 to 20	(c)	na	OMe	BOC-NHCH$_2$COO-	OtBDMS	sb	Et	OH	sb
24	17 to 20	(c)	na	OMe	tBDMS-OCH$_2$COO-	OtBDMS	sb	Et	OH	sb
25a	17 to 20	(c)	na	OMe	BOC-NHCH$_2$COO-	OH	sb	allyl	OH	sb
25b	17 to 20	(c)	na	OMe	OH	BOC-NHCH$_2$COO-	sb	allyl	OH	sb
25c	17 to 20	(c)	na	OMe	BOC-NHCH$_2$COO-	BOC-NHCH$_2$COO-	sb	allyl	OH	sb
25d	17,19,20	(c)	na	OMe	BOC-NHCH$_2$COO-	absent	db	allyl	OH	sb
26a	17 to 20	(c)	na	OMe	BOC-NHCH$_2$COO-	OH	sb	Et	OH	sb
26b	17 to 20	(c)	na	OMe	OH	BOC-NHCH$_2$COO-	sb	Et	OH	sb
26c	17 to 20	(c)	na	OMe	BOC-NHCH$_2$COO-	BOC-NHCH$_2$COO-	sb	Et	OH	sb
26d	17 to 20	(c)	na	OMe	BOC-NHCH$_2$COO-	absent	db	Et	OH	sb
27a	17 to 20	(c)	na	OMe	NH$_2$COCOO-	OH	sb	allyl	OH	sb
27b	17 to 20	(c)	na	OMe	NH$_2$COCOO-	NH$_2$COCOO-	sb	allyl	OH	sb
27c	17 to 20	(c)	na	OMe	NH$_2$COCOO-	absent	db	allyl	OH	sb
28a	17 to 20	(c)	na	OMe	NH$_2$COCOO-	OH	sb	Et	OH	sb
28b	17 to 20	(c)	na	OMe	NH$_2$COCOO-	NH$_2$COCOO-	sb	Et	OH	sb
28c	17 to 20	(c)	na	OMe	NH$_2$COCOO-	absent	db	Et	OH	sb
29	17 to 20	(c)	na	OMe	NH$_2$COCOO-	OtBDMS	sb	Et	OH	sb
30	17 to 20	(c)	na	OMe	NH$_2$COCOO-	OtBDMS	sb	allyl	OH	sb
31	17 to 20	(c)	na	OMe	p-tolyloxy-thiocarbonyloxy	OH	sb	Et	OH	sb
32	17 to 20	(c)	na	OMe	HOCH$_2$COO-	OH	sb	Et	OH	sb
33	17 to 20	(c)	na	OMe	tBDMS-OCH(CH$_3$)COO-(S)	OH	sb	Et	OH	sb
34	17 to 20	(c)	na	OMe	iBuoyloxy	OtBDMS	Et	OH	sb	
35	17 to 20	(c)	na	OMe	iBuoyloxy	OtBDMS	sb	allyl	OH	sb
36	17 to 20	(c)	na	OMe	iBuoyloxy	OH	sb	allyl	OH	sb
37	17 to 20	(c)	na	OMe	iBuoyloxy	OH	sb	Et	OH	sb
38	17,18,20	(c)	na	OMe	tBDMS-OCH(CH$_3$)COO-(S)	OtBDMS	sb	Et	OH	sb

Example 39: 24-tert-Butyldimethylsilyloxy-33-aminooxalyloxy-FK506

[Formula X: R_1 = a group (c) wherein R_6 = OMe, R_7 = aminooxalyloxy; R_2 = OtBDMS, single bond in 23,24 position; R_3 = allyl; R_4 = OH, single bond in 10,11 position]

A solution of **24,33-bis(tert-butyldimethylsilyloxy)-FK 506** in 70 ml of acetonitrile is reacted at 0° to 5° with 1 ml of oxalyl chloride and stirred at 0 to 5° for 40 minutes. The reaction mixture is stirred with a mixture of acetic acid ethyl ester and satured aqueous ammonia solution, any precipitate formed is sucked off, the phases are separated, the organic phase is washed successively with 1 N hydrochloric acid and then water, dried over sodium sulfate, filtered and concentrated under reduced pressure. From the residue the **title compound** is obtained as a colourless foamy resin following column chromatography over silicagel (eluant: n-hexane / acetic acid ethyl ester 1:1).

The following compounds of formula X are obtained in analogous manner as a colourless foamy resin:

Example No.	Analogous to Ex. No.	R_1	R_5	R_6	R_7	R_2	Position 23,24	R_3	R_4	Position 10,11
40	39[1)]	(c)	na	OMe	$NH_2COCOO-$	$NH_2COCOO-$	sb	allyl	OH	sb
41	39,40	(c)	na	OMe	$NH_2COCOO-$	OtBDMS	sb	Et	OH	sb
42	39,40	(c)	na	OMe	$NH_2COCOO-$	$NH_2COCOO-$	sb	Et	OH	sb

[1)] Stirring is effected for 1 hour at room temperature; column chromatography is effected using an eluant gradient of 3:1 to 1:3.

Example 43: 24-Methoxy-33-tert-butyldimethylsilyloxy-FK506

[Formula X: R_1 = a group (c) wherein R_6 = OMe, R_7 = OtBDMS; R_2 = OMe, single bond in 23,24 position; R_3 = allyl; R_4 = OH, single bond in 10,11 position]

1 g **33-tert-butyldimethylsilyloxy-FK 506** is dissolved into a mixture of 50 ml of dichloromethane and 0.04 ml of borotrifluoride etherate previously cooled to 0° to 5°. A solution of 20 ml of an approximately 1 N solution of diazomethane in methylene chloride is then added dropwise in such a manner that the yellow coloration of the solution which initially forms persists for as shortly as possible. The reaction mixture is diluted with acetic acid ethyl ester, successively washed with saturated aqueous sodium hydrogen carbonate solution and water, dried over sodium sulfate, filtered and the solvent is removed under reduced pressure. The **title compound** is obtained as a colourless foamy resin from the residue following column chromatographic purification over silicagel (eluant: acetic acid ethyl ester / n-hexane).

The following compounds of formula X are obtained in analogous manner as a colourless foamy resin:

Example No.	Analogous to Ex. No.	R_1	R_5	R_6	R_7	R_2	Position 23,24	R_3	R_4	Position 10,11
44	43[1)]	(c)	na	OMe	OMe	OtBDMS	sb	allyl	OH	sb

[1)] Starting from 24-tert-butyldimethylsilyloxy-FK 506.

Example 45: 24-tert-Butyldimethylsilyloxy-33-oxo-FR 520

[Formula X: R_1 = a group (c) wherein R_5 = OMe, R_7 = oxo; R_2 = OtBDMS, single bond in 23,24 position R_3 = Et; R_4 = OH, single bond in 10,11 position]

2 g **24-tert-butyldimethylsilyloxy-FR 520** and 1 g N-methylmorpholin-N-oxide are dissolved in 100 ml of methylene chloride, reacted with 5 g molecular sieve (Molsieb 4A) and the mixture is stirred for 15 minutes at room temperature. 0.15 g tetrapropylammonium perruthenate is added and stirring is continued for 3 more hours at room temperature. The mixture is concentrated, the residue is taken up in acetic acid ethyl ester and the solution successively washed with saturated aqueous sodium hydrogen sulfite solution, saturated aqueous sodium chloride and saturated aqueous copper sulfate solution, the organic phase is dried over sodium sulfate, filtered and concentrated under reduced pressure. The **title compound** is obtained from the residue following column chromatography over silicagel (eluant: n-hexane / acetic acid ethyl ester).

The following compounds of formula X are obtained in analogous manner as a colourless foamy resin:

Example No.	Analogous to Ex. No.	R_1	R_5	R_6	R_7	R_2	Position 23,24	R_3	R_4	Position 10,11
46	45[1)]	(c)	na	OMe	OtBDMS	oxo	sb	Et	OH	sb
46a	45[2)]	(c)	na	OMe	oxo	OtBDMS	sb	allyl	OH	sb
46b	45	(c)	na	OMe	OtBDMS	oxo	sb	allyl	OH	sb

[1)] Starting from 33-tert-butyldimethylsilyloxy-FR 520 (DOS 39 38 754);
[2)] Starting from 24-tert-butyldimethylsilyloxy-FK 506.

Example 47: 24-Oxo-FK 506

[Formula X: R_1 = a group (c) wherein R_6 = OMe, R_7 = OH; R_2 = oxo, single bond in 23,24 position; R_3 = allyl; R_4 = OH, single bond in 10,11 position]

3.6 g **24-oxo-33-tert-butyldimethylsilyloxy-FK506** (compound of Example 16b) is dissolved at room temperature into a mixture of 110 ml of acetonitrile and 3 ml of 40 % wt. aqueous hydrofluoric acid and the mixture is stirred at room temperature for 45 minutes. The reaction mixture is diluted with acetic acid ethyl ester, washed successively with saturated aqueous sodium bicarbonate solution and then water, dried over sodium sulfate, filtered and concentrated under reduced pressure. The **title compound** is obtained as a colourless foamy resin following chromatographic purification of the residue over silicagel (eluant: acetic acid ethyl ester / n-hexane 3:2).

The following compounds of formula X are obtained in analogous manner as a colourless foamy resin:

Example No.	Analogous to Ex. No.	R_1	R_5	R_6	R_7	R_2	Position 23,24	R_3	R_4	Position 10,11
48	47[1)]	(c)	na	OMe	NH_2CH_2COO-	OH	sb	allyl	OH	sb
49	47[2)]	(c)	na	OMe	NH_2CH_2COO-	absent	db	allyl	OH	sb
50	47[3)]	(c)	na	OMe	OH	oxo	sb	Et	OH	sb
51	47[4)]	(c)	na	OMe	NH_2CH_2COO-	OH	sb	Et	OH	sb
52	47[5)]	(c)	na	OMe	NH_2CH_2COO-	absent	db	Et	OH	sb
53	47[6)]	(c)	na	OMe	$HOCH_2COO-$	OH	sb	allyl	OH	sb
54	47[7)]	(c)	na	OMe	$HOCH_2COO-$	OH	sb	Et	OH	sb
55	47[8)]	(c)	na	OMe	$HOCH(CH_3)COO-$ (S)	OH	sb	Et	OH	sb
56	47[9)]	(c)	na	OMe	OH	NH_2CH_2COO-	sb	Et	OH	sb
57	47[10)]	(c)	na	OMe	NH_2CH_2COO-	NH_2CH_2COO-	sb	Et	OH	sb
58	47[11)]	(c)	na	OMe	NH_2CH_2COO-	NH_2CH_2COO-	sb	allyl	OH	sb
59	47[12)]	(c)	na	OMe	OH	NH_2CH_2COO-	sb	allyl	OH	sb
60	47[13)]	(c)	na	OMe	NH_2CH_2COO-	OH	sb	allyl	OH	sb
61	47[14)]	(c)	na	OMe	NH_2CH_2COO-	OH	sb	Et	OH	sb
62	47[15)]	(c)	na	OMe	iBuoyloxy	OH	sb	Et	OH	sb
63	47[16)]	(c)	na	OMe	iBuoyloxy	OH	sb	allyl	OH	sb

The following compounds of formula I are obtained in analogous manner in accordance with process variant deprotection:

Example No.	Analogous to Ex. No.	R_1	R_5	R_6	R_7	R_2	Position 23,24	R_3	R_4	Position 10,11	Physicochemical characterization data
64	47[17)]	(a)	I	OMe	na	OH	sb	Et	OH	sb	cfr; **
65a	47[18)]	(a)	Cl	OMe	na	OH	sb	allyl	OH	sb	cfr; NMR*
65b	47[18)]	(a)	Cl	OMe	na	OH	sb	allyl	absent	db	cfr
66a	47[19)]	(a)	Cl	OMe	na	OH	sb	Et	OH	sb	cfr; NMR*
66b	47[20)]	(a)	Cl	OMe	na	OH	sb	Et	absent	db	cfr; NMR*
67a	47[20)]	(a)	Br	OMe	na	OH	sb	Et	OH	sb	cfr; NMR
67b	47[21)]	(a)	Br	OMe	na	OH	sb	Et	absent	db	cfr
68a	47[21)]	(a)	N_3	OMe	na	OH	sb	allyl	OH	sb	cfr; NMR*
68b	47[22)]	(a)	N_3	OMe	na	OH	sb	allyl	absent	db	cfr; NMR
69a	47[22)]	(a)	Br	OMe	na	OH	sb	allyl	OH	sb	cfr
69b	47[23)]	(a)	Br	OMe	na	OH	sb	allyl	absent	db	cfr
70a	47[23)]	(a)	N_3	OMe	na	OH	sb	Et	OH	sb	cfr; NMR
70b	47	(a)	N_3	OMe	na	OH	sb	Et	absent	db	cfr

1)
2) Starting from the compound of Example 25a;
3) Starting from the compound of Example 25d;
4) Starting from the compound of Example 46 (=16d);
5) Starting from the compound of Example 23;
6) Starting from the compound of Example 26d;
7) Starting from the compound of Example 22;
8) Starting from the compound of Example 24;
9) Starting from the compound of Example 19 or of Example 33;
Starting from the compound of Example 26b;

10) Starting from the compound of Example 26c;
11) Starting from the compound of Example 25c;
12) Starting from the compound of Example 25b;
13) Starting from the compound of Example 25a;
14) Starting from the compound of Example 26a;
15) Starting from the compound of Example 34;
16) Starting from the compound of Example 35;
17) Starting from the compound of Example 6a;
18) Starting from the compound of Example 1;
19) Starting from the compound of Example 3;
20) Starting from the compound of Example 4;
21) Starting from the compound of Example 2;
22) Starting from the compound of Example 5;
23) Starting from the compound of Example 6;

* ^{1}H-NMR:

Example 48: about 2:1 mixture of conformers:
5.33 and 5.20 (d/d, J=1 Hz and 1 Hz, H-26); 4.84 (dxdxd, J=5 Hz, 9.5 Hz and 11 Hz, H-33); 3.44 (s, 2H, O=C-CH$_2$-N-); 3.22 (dxdxd, J=5 Hz, 9.5 Hz and 11 Hz, H-32);

Example 49: see Example 18;

Example 50: mixture of conformers:
5.8 and 5.6 (s/s, H-23); 5.69 (H-26); 4.38 (d, J=13 Hz, H-6e); 4.19 (t, H-2); 3.80 (dxd, J=9 Hz and 2 Hz, H-14);

Example 51: about 2:1 mixture of conformers:
5.34 (d, J=2 Hz, H-26); 4.75 (dxdxd, J=5 Hz, 9 Hz and 10 Hz, H-33); 4.61 (db, J=4 Hz, H-2); 4.44 (db, J=13 Hz, H-6e); 3.45 (s, -CH$_2$-N);

Example 53: ^{1}H-NMR: see Example 20;
Example 54: ^{1}H-NMR: see Example 32;
Example 55: ^{1}H-NMR: mixture of conformers: main conformer: 1.23 (d, J=7 Hz); 4.30 [dq, J_1=5 Hz, J_2=7 Hz, -COCH(CH_3)OH]; 4.44 (d, br, J=13 Hz, H-6e); 4.61 (d, br, J=4 Hz); 4.78 (ddd, J_1=5 Hz, J_2=5 Hz, J_3=11 Hz, H-33); 5.34 (H-26);
Example 60: ^{1}H-NMR: see Example 48;
Example 61: ^{1}H-NMR: see Example 51;
Example 62: ^{1}H-NMR: see Example 37;
Example 65a: ^{1}H-NMR 4.59 (m, H-33);
^{13}C-NMR: about 2:3 mixture of conformers:
main conformer: 59.1 (C-33; 79.2 (C-32); 97.5 (C-10); 116.4 (C-38); 123.0 (C-20); 135.6 (C-37); 138.4 (C-19); 164.6 (C-8); 168.9 (C-1); 196.4 (C-9); 209.4 (C-22);
Example 66a: ^{1}H-NMR: 4.56 (m, H-33);
Example 66b: ^{1}H-NMR: 2.09 (s, 11-CH_3); 4.5 (bm, H-33);
^{13}C-NMR: about 2:1 mixture of conformers:
main conformer: 56.2 (C-33); 80.6 (C-32); 116.4 (C-38); 122.9 (C-20); 124.8 (C-11); 129.5 (C-29); 131.9 (C-28): 135.8 (C-37); 140.0 (C-19); 142.9 (C-10); 166.7 (C-8); 168.7 (C-1); 188.0 (C-9); 212.4 (C-22);
minor conformer: 56.1 (C-33); 80.6 (C-32); 116.5 (C-38); 123.6 (C-20); 126.4 (C-11); 128.5 (C-29); 131.8 (C-28); 135.6 (C-37); 137.4 (C-19); 144.1 (C-10); 166.5 (C-8); 169.5 (C-1); 184.8 (C-9); 213.3 (C-22);
Example 67a: ^{1}H-NMR: 4.44 (d, J=13 Hz, H-6 eq.); 4.60 (d, J=4 Hz, H-2); 4.70 (sb, H-33);
Example 68a: ^{1}H-NMR: 4.07 (m, $w_{1/2}$ = 8 Hz, H-33);
Example 68b: ^{1}H-NMR: about 2:1 mixture of conformers: 4.06 (m, H-33); 2.09 and 1.94 (2s, 11-CH_3);
Example 70a: ^{1}H-NMR: about 5:4 mixture of conformers: 5.60 resp. 5.79 (s resp. s, H-23); 5.70 resp. 5.66 (d, J=3 Hz resp. d, J=3 Hz, H-26); 4.38 (d, J=13 Hz, H-6e); 4.15 (t, H-2); 3.80 (dxd, J=9 Hz and 2 Hz, H-14).

** Iodine analyis: theor.: 14.06 %; found: 13.57 %.

The compounds of Examples 10a, 11a, 12 and 13 may be prepared in analogous manner according to process variant deprotection.

Example 71: 24-tert-Butyldimethylsilyloxy-29-des-(4-hydroxy-3-methylcyclohexyl)-29-(3-formyl-cyclopentyl)-FR 520

[Formula I: R_1 = a group (d); R_2 = OtBDMS, single bond in 23,24 position; R_3 = Et; R_4 = OH, single bond in 10,11 position]

[Process variant protection]

A solution of 1.2 g **29-des-(4-hydroxy-3-methylcyclohexyl)-29-(3-formylcyclopentyl)-FR 520** - (compound of Example 12), 1.5 g tert-butyldimethylsilyl chloride and 0.8 g imidazole in 20 ml of dry dimethylformamide is stirred for 15 hours at room temperature and thereafter partitioned between 1 N hydrochloric acid solution and acetic acid ethyl ester. The organic phase is separated, washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and concentrated under reduced pressure. The **title compound** is obtained from the residue as a colourless foamy resin following column chromatography over silicagel (eluant: n-hexane / acetic acid ethyl ester):

^{1}H-NMR: mixture of rotamers: 9.65 (d, J = 2 Hz, CHO); 5.39 (d, J = 9 Hz, H-29); 5.01 (d, J = 7.5 Hz, H-26); 4.81 (d, J = 10 Hz, H-20); 3.82 (dxd, J = 9/2 Hz, H-24).

The compounds of Examples 1 to 9 may be prepared in analogous manner according to process variant protection.

The compounds of the invention possess pharmacological activity. They are indicated for use as pharmaceuticals. In particular they possess antiinflammatory, and immunosuppressant and antiproliferative activity.

Antiinflammatory activity may e.g. be determined in the following test methods:

1. Oxazolone allergic contact dermatitis in the mouse in vivo upon topical application: the test method is as described in F.M. Dietrich and R. Hess, Int. Arch. Allergy 38 (1970) 246-259. The compounds elicit in this test an activity between about 15 % and about 68 % upon topical administration at a concentration of about 0.01 %.

2. DNFB allergy (swine): the test method is as described in e.g. EP 315978. Topical application of a 1.2 % formulation of the compounds repeated twice results in from about 36 % to about 40 % inhibition of the inflammatory reaction.

Immunosuppressant and antiproliferative activity may e.g. be determined in the following test methods:

1. Proliferative response of lymphocytes to allogen stimulation in the mixed lymphocyte reaction (MLR) in vitro: T. Meo, "The MLR in the Mouse", Immunological Methods, L. Lefkovits and B. Pernis, Eds., Academic Press, N.Y. (1979), 227-239.

The compounds elicit in this test (IC_{50}) suppression of mixed lymphocytes at a dosage of from about < 0.0008 µg/ml to about 0.09 µg/ml.

2. Inhibition of the primary humoral immune response to sheep erythrocytes in vitro: the test method is as described in R.I. Mishell and R.W. Dutton, Science 153 (1966) 1004-1006; R.I. Mishell and R.W. Dutton, J. Exp. Med. 126 (1967) 423-442.

The compounds are active in this test with an IC_{50} of from about 0.0024 µg/ml to about 0.32 µg/ml.

3. Inhibition of proliferation of human keratinocytes: the test method is as described in e.g. EP 315978. The compounds are active in this test at concentrations of from about 1 µg/ml to about 10 µg/ml resulting in an inhibition of from about 30 % to about 90 %.

The compounds of the invention in free form and where such forms exist in pharmaceutically acceptable salt form are therefore indicated as antiinflammatory and as immunosuppressant and antiproliferative agents for use in the prevention and treatment of inflammatory conditions and of conditions requiring immunosuppression, such as

a) the prevention and treatment of
- resistance in situations of organ or tissue transplantation, e.g. of heart, kidney, liver, bone marrow and skin,
- graft-versus-host disease, such as following bone marrow grafts,
- autoimmune diseases such as rheumatoid arthritis, systemic Lupus erythematosus, Hashimoto's thyroidis, multiple sclerosis, Myasthenia gravis, diabetes type I and uveitis,
- cutaneous manifestations of immunologically-mediated illnesses;

b) the treatment of inflammatory and hyperproliferative skin diseases, such as psoriasis, atopical dermatitis, contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis, Lichen planus, Pemphigus, bullous Pemphigoid, Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, Lupus erythematosus and acne; and

c) Alopecia areata.

The compounds may be administered systemically or topically.

For these indications the appropriate dosage will, of course, vary depending upon, for example, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.15 mg/kg to about 1.5 mg/kg animal body weight. An indicated daily dosage in the larger mammal is in the range from about 0.01 mg to about 100 mg, conveniently administered, for example, in divided doses up to four times a day or in retard form.

For topical use satisfactory results are obtained with local administration of a 1-3 % concentration of active substance several times daily, e.g. 2 to 5 times daily. Examples of indicated galenical forms are lotions, gels and creams.

The compounds of the invention may be administered by any conventional route, in particular enterally, e.g. orally, e.g. in the form of tablets or capsules, or topically, e.g. in the form of lotions, gels or creams.

Pharmaceutical compositions comprising a compound of the invention in association with at least one pharmaceutical acceptable carrier or diluent may be manufactured in conventional manner by mixing with a pharmaceutically acceptable carrier or diluent. Unit dosage forms contain, for example, from about 0.0025 mg to about 50 mg of active substance.

Topical administration is e.g. to the skin. A further form of topical administration is to the eye, for the treatment of immune-mediated conditions of the eye, such as: auto-immune diseases, e.g. uveitis, keratoplasty and chronic keratitis; allergic conditions, e.g. vernal conjunctivitis; inflammatory conditions and corneal transplants, by the topical administration to the eye surface of a compound of the invention in a pharmaceutically acceptable ophthalmic vehicle.

The ophthalmic vehicle is such that the compound is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye, e.g. the anterior chamber, posterior chamber, vitreous body, aqueous humor, vitreous humor, cornea, iris/ciliary, lens, choroid/retina and sclera.

The pharmaceutically acceptable ophthalmic vehicle may be e.g. an ointment, vegetable oil, or an encapsulating material.

Whilst the antiinflammatory and immunosuppressant and antiproliferative activity is the main activity of the compounds of the invention they also possesses some degree of activity in increasing sensitivity to, or in increasing the efficacy of, chemotherapeutic drug therapy.

This activity may e.g. be determined according to the test methods described in EP 360760.

The compounds of the invention are therefore indicated for use in reversing chemotherapeutic drug resistance of varying types, e.g. acquired or innate, or in increasing sensitivity to administered drug therapy, e.g. as a means of reducing regular chemotherapeutic dosage levels, for example in the case of anti-neoplastic or cytostatic drug therapy, as a means of decreasing overall drug toxicity and, more especially, as a means of reversing or reducing resistance, including both inherent and acquired resistance, to chemotherapy.

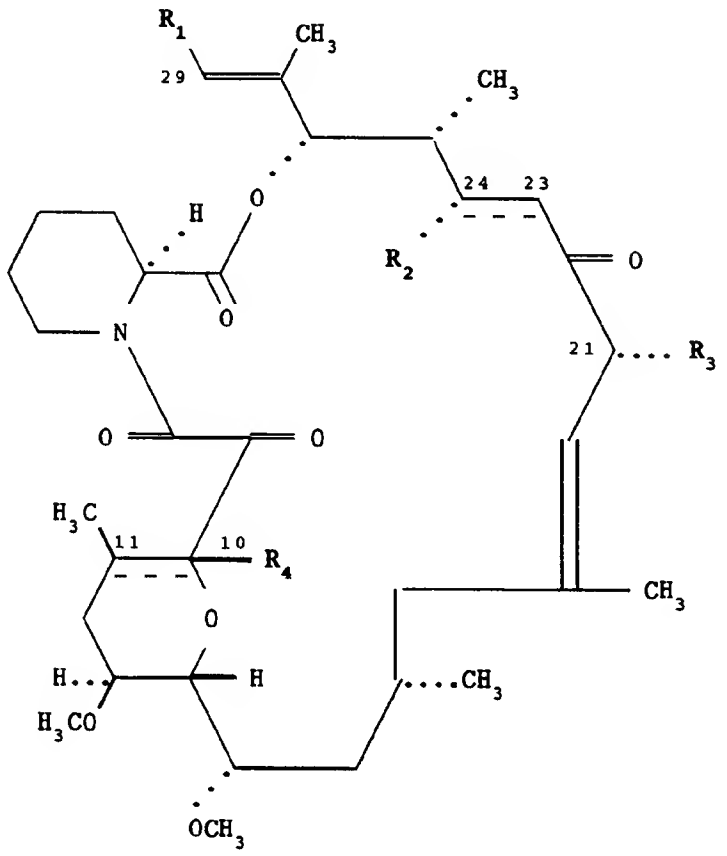
Preferred in the above indications are the following compounds of the invention:

- 29-des-(4-hydroxy-3-methoxycyclohexyl)-29-(3-formylcyclopentyl)-FR 520 (compound of Example 12); and
- 33-epi-33-chloro-FR 520 (compound of Example 66a).

Claims

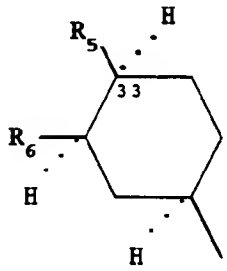
Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. A compound of formula I



I

wherein
either
R_1 is a group (a) of formula

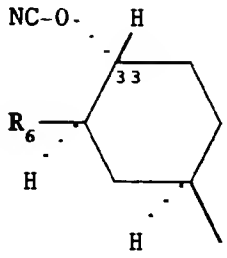


(a)

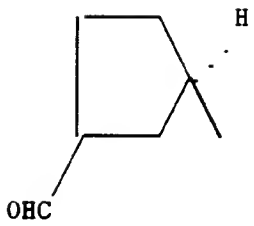
wherein
R_5 is chloro, bromo, iodo or azido and
R_6 is hydroxy or methoxy;
R_2 is oxo and there is a single bond in 23,24 position; optionally protected hydroxy and there is a single or a double bond in 23,24 position; or absent and there is a double bond in 23,24 position; and
R_4 is hydroxy and there is a single bond in 10,11 position; or absent and there is a double bond in 10,11 position;

or

R_1 is a group (b) or (d) of formula



(b) and



(d)

wherein

R_6 is as defined above;

R_2 is as defined above; and

R_4 is hydroxy and there is a single bond in 10,11 position; and

R_3 is methyl, ethyl, n-propyl or allyl;

in free form or, where such forms exist, in salt form.

2. A compound according to claim 1 which is a **compound Ip_1**,
i.e. a compound of formula I wherein

R_1 is a group (a) wherein R_6 is methoxy and

either

R_5 is chloro or bromo and

R_4 is hydroxy and there is a single bond in 10,11 position

or

R_5 is azido and

R_4 is hydroxy and there is a single bond in 10,11 position or absent and there is a double bond in 10,11 position;

R_2 is optionally protected hydroxy and there is a single or a double bond in 23,24 position; and

R_3 is as defined in claim 1;

in free form or, where such forms exist, in salt form.

3. A compound according to claim 1 which is a **compound Ip_3**,
i.e. a compound of formula I wherein

R_1 is a group (b) wherein R_6 is methoxy,

R_2 is optionally protected hydroxy and there is a single bond in 23,24 position; or absent and there is a double bond in 23,24 position;

R_4 is hydroxy and there is a single bond in 10,11 position; and

R_3 is as defined in claim 1;

in free form or, where such forms exist, in salt form.

4. A compound according to claim 1 which is a **compound Ip_4**,
i.e. a compound of formula I wherein

R_1 is a group (d),

R_2 is optionally protected hydroxy and there is a single bond in 23,24 position; or absent and there is a double bond in 23,24 position;

R_4 is hydroxy and there is a single bond in 10,11 position; and

R_3 is as defined in claim 1;

in free form or, where such forms exist, in salt form.

5. A compound of formula I according to claim 1 wherein R, is a group (d); R_2 is hydroxy and there is a single bond in 23,24 position; R_3 is ethyl; and R_4 is hydroxy and there is a single bond in 10,11 position; which is 29-des(4-hydroxy-3-methoxycyclohexyl)-29-(3-formylcyclopentyl)-FR 520 (compound of Example 12).

6. A compound of formula I according to claim 1 wherein R_1 is a group (a) wherein R_5 is chloro and R_6 is methoxy; R_2 is hydroxy and there is a single bond in 23,24 position; R_3 is ethyl; and R_4 is hydroxy and there is a single bond in 10,11 position; which is 33-epi-33-chloro-FR 520 (compound of Example 66a).

7. A process for the preparation of a compound according to claim 1 comprising

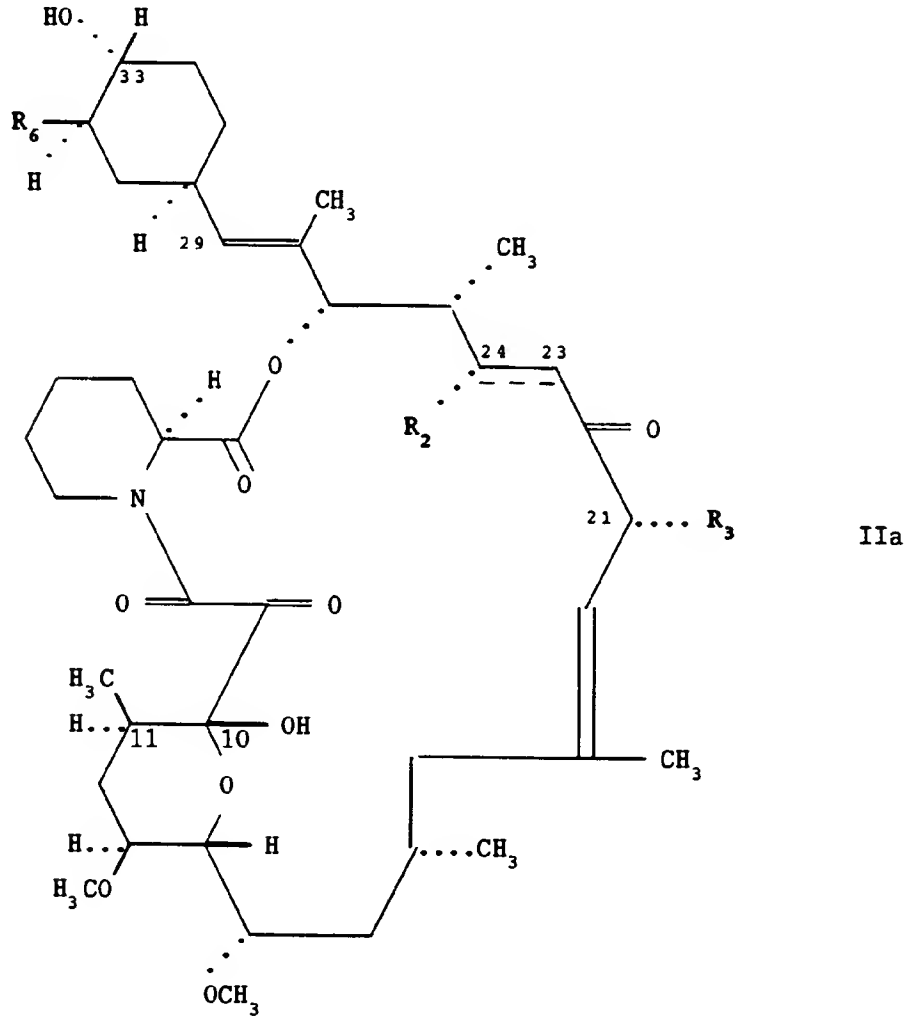
a) for the preparation of a compound of formula I wherein

R_1 is a group (a) as defined in claim 1,

R_2 and R_3 are as defined in claim 1 and

R_4 is hydroxy (i.e. a **compound Ia**),

replacing under simultaneous epimerization the hydroxy group by chlorine, bromine, iodine or azido in a corresponding compound having unprotected hydroxy in 33 position (i.e. a **compound IIa**, of formula IIa



IIa

wherein R_2 and R_3 are as defined in claim 1 under formula I and R_6 is hydroxy or methoxy);

b) for the preparation of a compound of formula I wherein

R_1 is a group (b) as defined in claim 1,

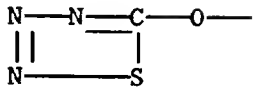
R_2 and R_3 are as defined in claim 1 and

R_4 is hydroxy

(i.e. a **compound Ib**),

treating a corresponding compound IIa with cyanogen bromide in the presence of a base or

treating a corresponding compound IIa with thiophosgene, reacting the resultant product with an inorganic aside and allowing the resultant unstable intermediate having a group



in 33 position (i.e. a **compound IIb**) to decompose to a corresponding compound Ib;

c) for the preparation of a compound of formula I wherein

R_1 is a group (d) as defined in claim 1,

R_2 and R_3 are as defined in claim 1 and

R_4 is hydroxy

(i.e. a **compound Ic**),

treating a corresponding compound Ib with an acid having a non-nucleophilic anion; and

- when a resultant compound of formula I has a protected hydroxy and/or a protected amino group, optionally splitting off the protecting group(s) to give a corresponding compound of formula I having one or more unprotected hydroxy and/or unprotected amino group(s) (i.e. a **compound Ij**),

  whereby when R_1 is a group (a), a water molecule may be simultaneously split off and a compound of formula I is obtained wherein

  R_1 is a group (a) as defined in claim 1,

  R_2 is unprotected hydroxy and there is a single or double bond in 23,24 position; and

  R_4 is absent and there is a double bond in 10,11 position

  (i.e. a **compound Il**); or

- optionally protecting an unprotected hydroxy and/or unprotected amino group in a resultant compound of formula I as appropriate to give a corresponding compound of formula I having one or more protected hydroxy and/or protected amino groups(s) (i.e. a **compound Ik**);

and recovering the resultant compound of formula I in free form and, where such forms exist, in salt form.

8. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6 in free form or, where such forms exist, in pharmaceutically acceptable salt form, together with a pharmaceutically acceptable carrier or diluent.

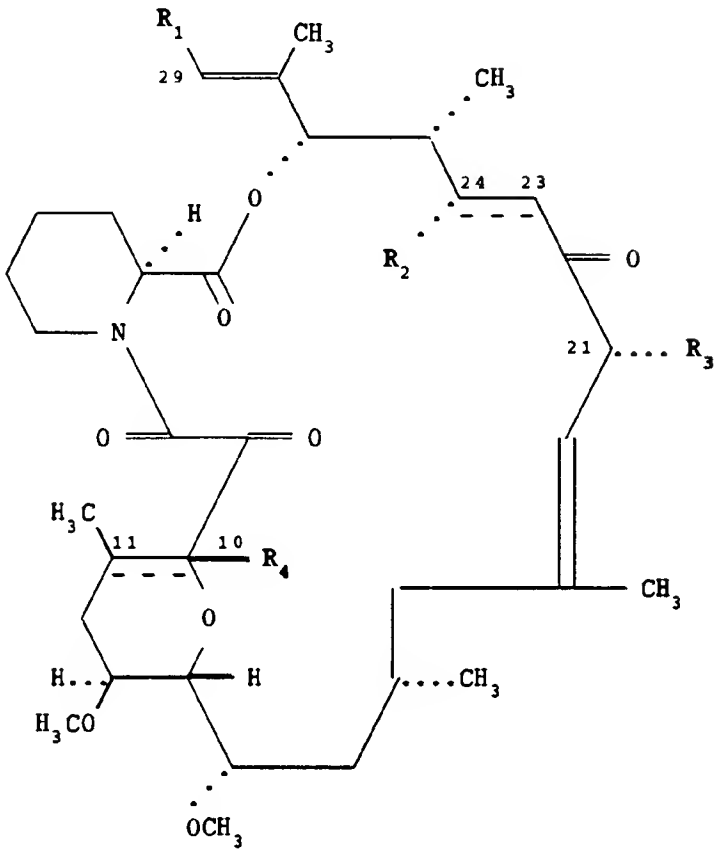
9. A compound according to any one of claims 1 to 6 in free form or, where such forms exist, in pharmaceutically acceptable salt form, for use as a pharmaceutical.

10. A compound according to claim 9 for use in the preparation of a pharmaceutical composition by mixing with a pharmaceutically acceptable carrier or diluent.

11. A process for the preparation of a pharmaceutical composition comprising mixing a compound according to any one of claims 1 to 6 in free form or, where such forms exist, in pharmaceutically acceptable salt form, with a pharmaceutically acceptable carrier or diluent.

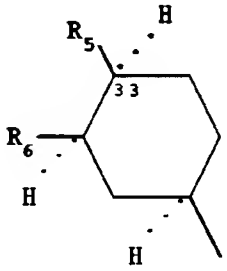
Claims for the following Contracting States : ES, GR

1. A process for the preparation of a compound of formula I



I

wherein
either
R_1 is a group (a) of formula

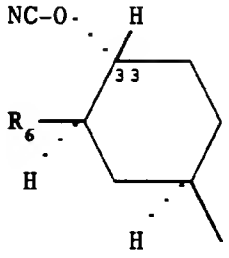


(a)

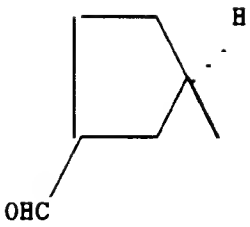
wherein
R_5 is chloro, bromo, iodo or azido and
R_6 is hydroxy or methoxy;
R_2 is oxo and there is a single bond in 23,24 position; optionally protected hydroxy and there is a single or a double bond in 23,24 position; or absent and there is a double bond in 23,24 position; and
R_4 is hydroxy and there is a single bond in 10,11 position; or absent and there is a double bond in 10,11 position;

or

R_1 is a group (b) or (d) of formula



(b) and



(d)

wherein

R_6 is as defined above;

R_2 is as defined above; and

R_4 is hydroxy and there is a single bond in 10,11 position; and

R_3 is methyl, ethyl, n-propyl or allyl;

in free form or, where such forms exist, in salt form,

comprising

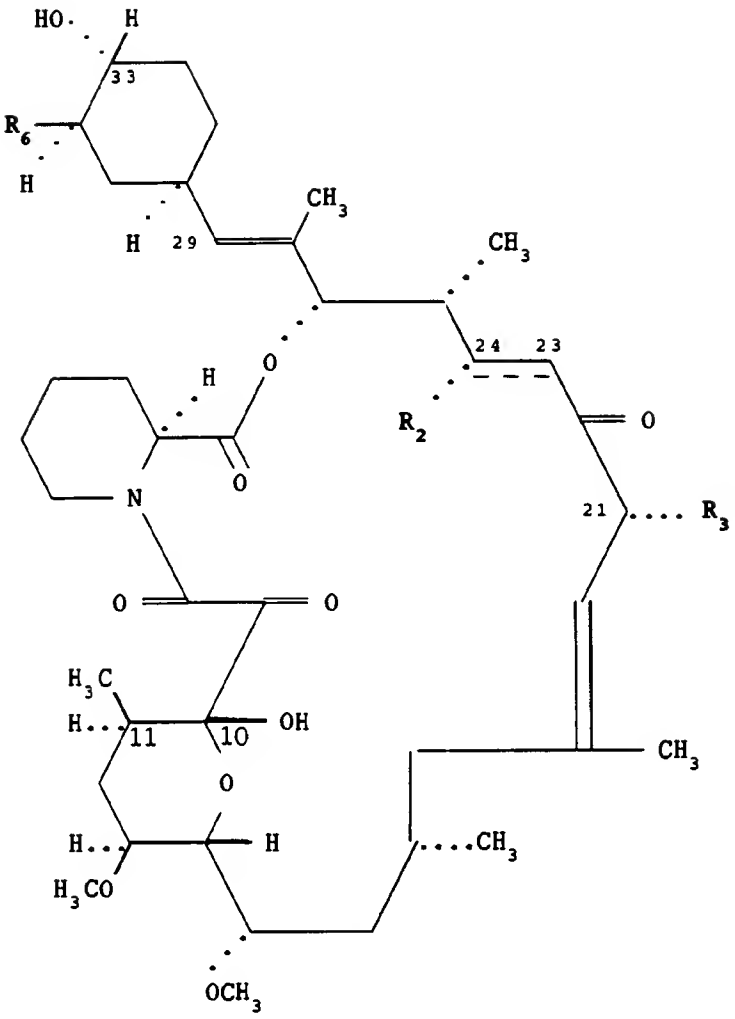
a) for the preparation of a compound of formula I wherein

R_1 is a group (a) as defined in claim 1,

R_2 and R_3 are as defined in claim 1 and

R_4 is hydroxy (i.e. a **compound Ia**),

replacing under simultaneous epimerization the hydroxy group by chlorine, bromine, iodine or azido in a corresponding compound having unprotected hydroxy in 33 position (i.e. a **compound IIa**, of formula IIa



IIa

wherein R_2 and R_3 are as defined above under formula I and R_6 is hydroxy or methoxy);

b) for the preparation of a compound of formula I wherein

R_1 is a group (b) as defined in claim 1,

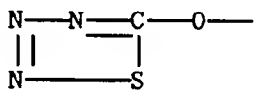
R_2 and R_3 are as defined in claim 1 and

R_4 is hydroxy

(i.e. a **compound Ib**),

treating a corresponding compound IIa with cyanogen bromide in the presence of a base or

treating a corresponding compound IIa with thiophosgene, reacting the resultant product with an inorganic aside and allowing the resultant unstable intermediate having a group



in 33 position (i.e. a **compound IIb**) to decompose to a corresponding compound Ib;

c) for the preparation of a compound of formula I wherein

R_1 is a group (d) as defined in claim 1,

R_2 and R_3 are as defined in claim 1 and

R_4 is hydroxy

(i.e. a **compound Ic**),

treating a corresponding compound Ib with an acid having a non-nucleophilic anion; and

- when a resultant compound of formula I has a protected hydroxy and/or a protected amino group, optionally splitting off the protecting group(s) to give a corresponding compound of formula I having one or more unprotected hydroxy and/or unprotected amino group(s) (i.e. a **compound Ij**),

  whereby when R_1 is a group (a), a water molecule may be simultaneously split off and a compound of formula I is obtained wherein

  R_1 is a group (a) as defined in claim 1,

  R_2 is unprotected hydroxy and there is a single or double bond in 23,24 position; and

  R_4 is absent and there is a double bond in 10,11 position

  (i.e. a **compound Ii**); or
- optionally protecting an unprotected hydroxy and/or unprotected amino group in a resultant compound of formula I as appropriate to give a corresponding compound of formula I having one or more protected hydroxy and/or protected amino groups(s) (i.e. a **compound Ik**);

and recovering the resultant compound of formula I in free form and, where such forms exist, in salt form.

2. A process according to claim 1 for the preparation of the compound of formula I wherein R_1 is a group (d); R_2 is hydroxy and there is a single bond in 23,24 position; R_3 is ethyl; and R_4 is hydroxy and there is a single bond in 10,11 position; which is 29-des-(4-hydroxy-3-methoxycyclohexyl)-29-(3-formyl-cyclopentyl)-FR 520 (compound of Example 12).

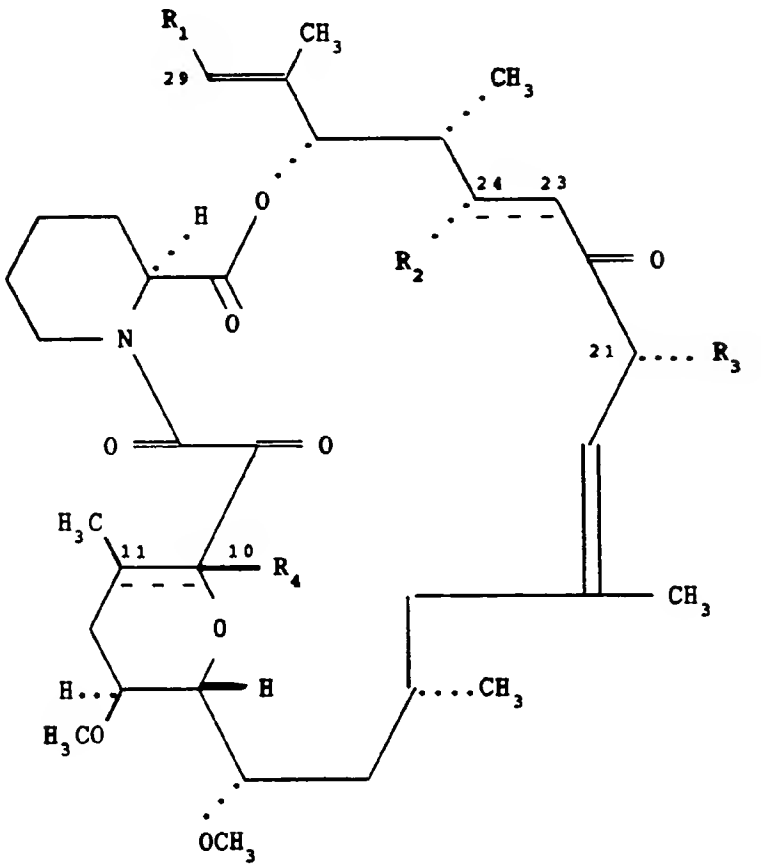
3. A process according to claim 1 for the preparation of the compound of formula I wherein R_1 is a group (a) wherein R_5 is chloro and R_6 is methoxy; R_2 is hydroxy and there is a single bond in 23,24 position; R_3 is ethyl; and R_4 is hydroxy and there is a single bond in 10,11 position; which is 33-epi-33-chloro-FR 520 (compound of Example 66a).

4. A process for the preparation of a pharmaceutical composition comprising mixing a compound of formula I as defined in claim 1 in free form or, where such forms exist, in pharmaceutically acceptable salt form, with a pharmaceutically acceptable carrier or diluent.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

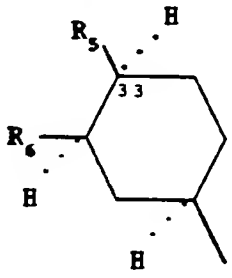
1. Verbindung der Formel I



I

worin entweder

R_1 eine Gruppe (a) der Formel



(a)

ist, worin

R_5 Chlor, Brom, Iod oder ein Azidorest ist und

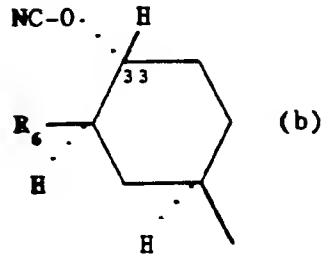
R_6 ein Hydroxy- oder Methoxyrest ist;

R_2 ein Oxorest ist und in Position 23, 24 eine Einfachbindung ist; ein gegebenenfalls geschützter Hydroxyrest ist und in Position 23, 24 eine Einfach- oder Doppelbindung ist; oder nicht vorhanden ist und in Position 23, 24 eine Doppelbindung ist; und

R_4 ein Hydroxyrest ist und in Position 10, 11 eine Einfachbindung ist; oder nicht vorhanden ist und in Position 10, 11 eine Doppelbindung ist;

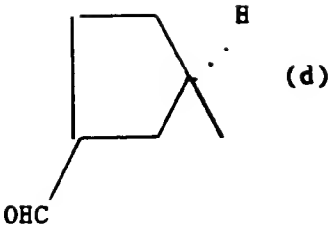
oder

R_1 eine Gruppe (b) oder (d) der Formel



(b)

und



(d)

ist, worin R_6 wie oben definiert ist;

R_2 wie oben definiert ist; und

R_4 ein Hydroxyrest ist und eine Einfachbindung in Position 10, 11 ist; und

R_3 ein Methyl-, Ethyl-, n-Propyl- oder Allylrest ist;

in freier Form oder, wenn diese Formen existieren, in Salzform.

2. Verbindung nach Anspruch 1, die eine Verbindung Ip_1 ist, d.h. eine Verbindung der Formel I, worin

R_1 eine Gruppe (a) ist, worin R_6 ein Methoxyrest ist und entweder

R_5 Chlor oder Brom ist und

R_4 ein Hydroxyrest ist und in Position 10, 11 eine Einfachbindung ist oder

R_5 ein Azidorest ist und

R_4 ein Hydroxyrest ist und in Position 10, 11 eine Einfachbindung ist, oder nicht vorhanden ist und in Position 10, 11 eine Doppelbindung ist;

R_2 ein gegebenenfalls geschützter Hydroxyrest ist und in Position 23, 24 eine Einfach- oder Doppelbindung ist; und

R_3 wie in Anspruch 1 definiert ist;

in freier Form oder, wenn diese Formen existieren, in Salzform.

3. Verbindung nach Anspruch 1, die eine Verbindung Ip_3 ist, d.h. eine Verbindung der Formel I, worin

R_1 eine Gruppe (b) ist, worin R_6 ein Methoxyrest ist,

R_2 ein gegebenenfalls geschützter Hydroxyrest ist und in Position 23, 24 eine Einfachbindung ist; oder nicht vorhanden ist und in Position 23, 24 eine Doppelbindung ist;

R_4 ein Hydroxyrest ist und in Position 10, 11 eine Einfachbindung ist; und

R_3 wie in Anspruch 1 definiert ist;

in freier Form oder, wenn diese Formen existieren, in Salzform.

4. Verbindung nach Anspruch 1, die eine Verbindung Ip_4 ist, d.h. eine Verbindung der Formel I, worin

R_1 eine Gruppe (d) ist,

R_2 ein gegebenenfalls geschützter Hydroxyrest ist und in Position 23, 24 eine Einfachbindung ist; oder nicht vorhanden ist und in Position 23, 24 eine Doppelbindung ist;

R_4 ein Hydroxyrest ist und in Position 10, 11 eine Einfachbindung ist; und

R_3 wie in Anspruch 1 definiert ist;

in freier Form oder, wenn diese Formen existieren, in Salzform.

5. Verbindung der Formel I nach Anspruch 1, worin R_1 eine Gruppe (d) ist; R_2 ein Hydroxyrest ist und in Position 23, 24 eine Einfachbindung ist; R_3 ein Ethylrest ist; und R_4 ein Hydroxyrest ist und in Position 10, 11 eine Einfachbindung ist; die 29-des-(4-Hydroxy-3-methoxycyclohexyl)-29-(3-formylcyclo-pentyl)-FR 520 (Verbindung von Beispiel 12) ist.

6. Verbindung der Formel I nach Anspruch 1, worin R_1 eine Gruppe (a) ist, worin R_5 Chlor ist und R_6 ein Methoxyrest ist; R_2 ein Hydroxyrest ist und in Position 23, 24 eine Einfachbindung ist; R_3 ein Ethylrest ist; und R_4 ein Hydroxyrest ist und in Position 10, 11 eine Einfachbindung ist; die 33-epi-33-Chlor-FR 520 (Verbindung von Beispiel 66a) ist.

7. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, umfassend,

a) zur Herstellung einer Verbindung der Formel I, worin

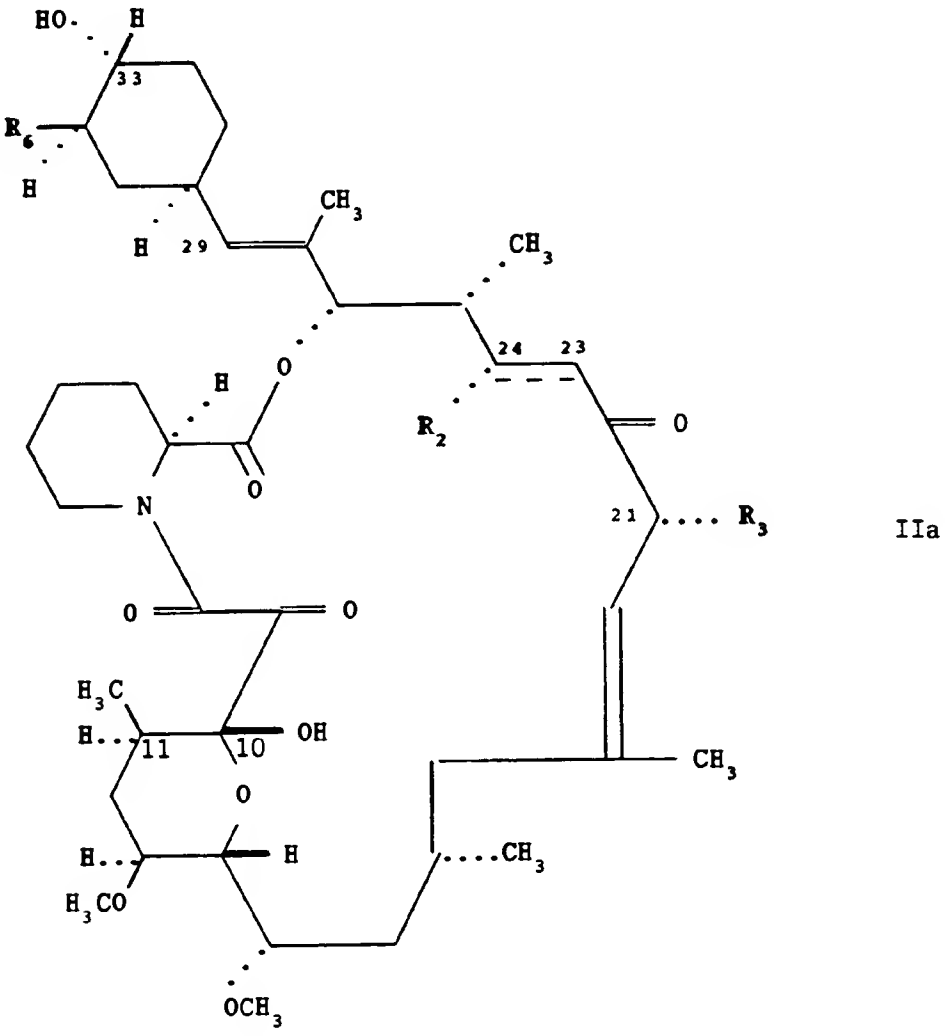
R_1 eine Gruppe (a), wie in Anspruch 1 definiert, ist,

R_2 und R_3 wie in Anspruch 1 definiert sind und

R_4 ein Hydroxyrest ist

(d.h. eine Verbindung Ia),

daß man unter gleichzeitiger Epimerisierung die Hydroxygruppe durch Chlor, Brom, Iod oder einen Azidorest in einer entsprechenden Verbindung mit einem ungeschützten Hydroxyrest in Position 33 ersetzt (d.h. eine Verbindung IIa der Formel IIa



IIa

worin R_2 und R_3 wie in Anspruch 1 für Formel I definiert sind und R_6 ein Hydroxy- oder Methoxyrest ist);

b) zur Herstellung einer Verbindung der Formel I, worin

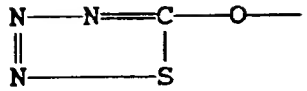
R_1 eine Gruppe (b), wie in Anspruch 1 definiert, ist,

R_2 und R_3 wie in Anspruch 1 definiert sind und

R_4 ein Hydroxyrest ist

(d.h. eine Verbindung Ib),

daß man eine entsprechende Verbindung IIa mit Bromcyan in Gegenwart einer Base behandelt oder eine entsprechende Verbindung IIa mit Thiophosgen versetzt, das entstehende Produkt mit einem anorganischen Azid umsetzt und das entstehende instabile Zwischenprodukt mit einer Gruppe



in Position 33 (d.h. eine Verbindung IIb) sich zu der entsprechenden Verbindung Ib zersetzen läßt;

c) zur Herstellung einer Verbindung der Formel I, worin

R_1 eine Gruppe (d), wie in Anspruch 1 definiert, ist,

R_2 und R_3 wie in Anspruch 1 definiert sind und

R_4 ein Hydroxyrest ist

(d.h. eine Verbindung Ic),

daß man eine entsprechende Verbindung Ib mit einer Säure mit einem nicht-nukleophilen Anion versetzt, und

- wenn eine entstehende Verbindung der Formel I eine geschützte Hydroxy- und/oder geschützte Aminogruppe hat, gegebenenfalls die Schutzgruppe(n) abspaltet, was eine entsprechende Verbindung der Formel I ergibt mit einer oder mehreren ungeschützten Hydroxy- und/oder ungeschützten Aminogruppen
(d.h. eine Verbindung Ij),
wobei dann, wenn R_1 eine Gruppe (a) ist, gleichzeitig ein Wassermolekül abgespalten werden kann und eine Verbindung der Formel I erhalten wird, worin
R_1 eine Gruppe (a), wie in Anspruch 1 definiert, ist,
R_2 ein ungeschützter Hydroxyrest ist und in Position 23, 24 eine Einfach- oder Doppelbindung ist; und
R_4 nicht vorhanden ist und in Position 10, 11 eine Doppelbindung ist
(d.h. eine Verbindung Ii); oder
- gegebenenfalls eine ungeschützte Hydroxy- und/oder ungeschützte Aminogruppe in einer entstehenden Verbindung der Formel I schützt, was eine entsprechende Verbindung der Formel I ergibt mit einer oder mehreren geschützten Hydroxy- und/oder geschützten Aminogruppen
(d.h. eine Verbindung Ik),

und die entstehende Verbindung der Formel I in freier Form und, wenn diese Formen existieren, in Salzform gewinnt.

8. Pharmazeutische Zusammensetzung, umfassend eine Verbindung nach einem der Ansprüche 1 bis 6 in freier Form oder, wenn diese Formen existieren, in Form des pharmazeutisch annehmbaren Salzes zusammen mit einem pharmazeutisch annehmbaren Träger oder Verdünnungsmittel.

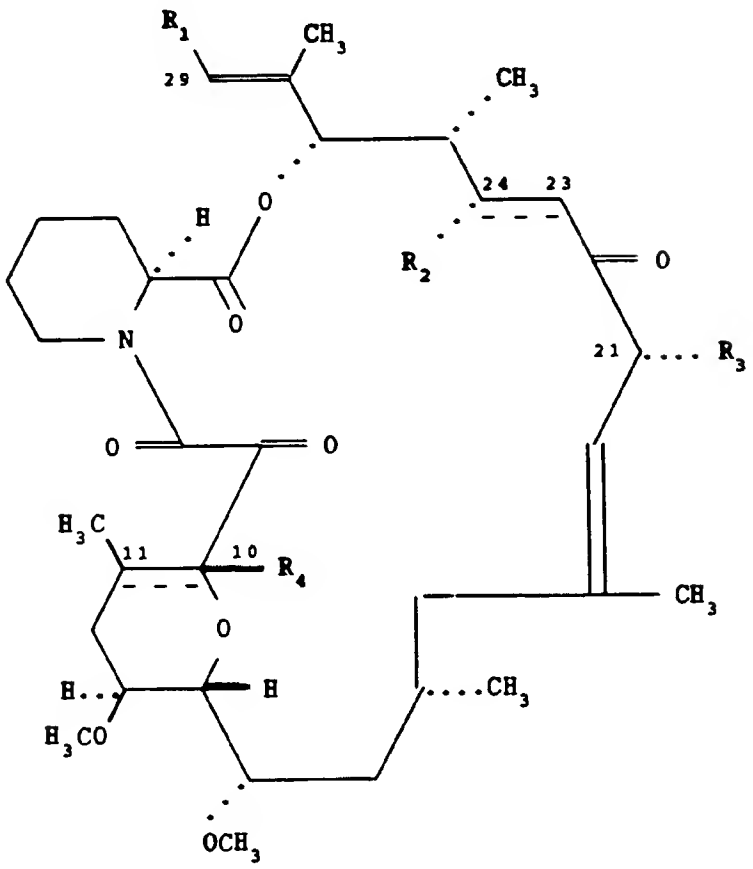
9. Verbindung nach einem der Ansprüche 1 bis 6 in freier Form oder, wenn diese Formen existieren, in Form des pharmazeutisch annehmbaren Salzes zur Vervendung als Pharmazeutikum.

10. Verbindung nach Anspruch 9 zur Verwendung zur Herstellung einer pharmazeutischen Zusammensetzung, indem sie mit einem pharmazeutisch annehmbaren Träger oder Verdünnungsmittel vermischt wird.

11. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, umfassend, daß man eine Verbindung nach einem der Ansprüche 1 bis 6 in freier Form oder, wenn diese Formen existieren, in Form des pharmazeutisch annehmbaren Salzes mit einem pharmazeutisch annehmbaren Träger oder Verdünnungsmittel vermischt.

Patentansprüche für folgende Vertragsstaaten : ES und GR

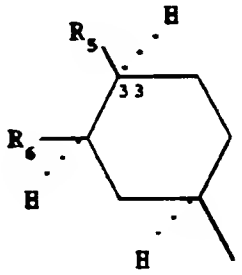
1. Verfahren zur Herstellung einer Verbindung der Formel I



I

worin entweder

R_1 eine Gruppe (a) der Formel



(a)

ist, worin

R_5 Chlor, Brom, Iod oder ein Azidorest ist und

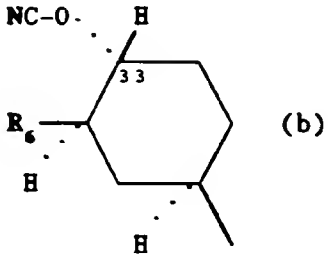
R_6 ein Hydroxy- oder Methoxyrest ist;

R_2 ein Oxorest ist und in Position 23, 24 eine Einfachbindung ist; ein gegebenenfalls geschützter Hydroxyrest ist und in Position 23, 24 eine Einfach- oder Doppelbindung ist; oder nicht vorhanden ist und in Position 23, 24 eine Doppelbindung ist; und

R_4 ein Hydroxyrest ist und in Position 10, 11 eine Einfachbindung ist; oder nicht vorhanden ist und in Position 10, 11 eine Doppelbindung ist;

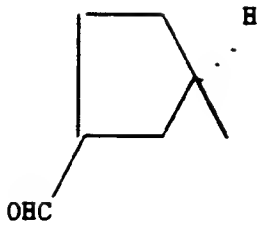
oder

R_1 eine Gruppe (b) oder (d) der Formel



(b)

und



(d)

ist, worin R_6 wie oben definiert ist;

R_2 wie oben definiert ist; und

R_4 ein Hydroxyrest ist und eine Einfachbindung in Position 10, 11 ist; und

R_3 ein Methyl-, Ethyl-, n-Propyl- oder Allylrest ist;

in freier Form oder, wenn diese Formen existieren, in Salzform, umfassend, daß man

a) zur Herstellung einer Verbindung der Formel I, worin

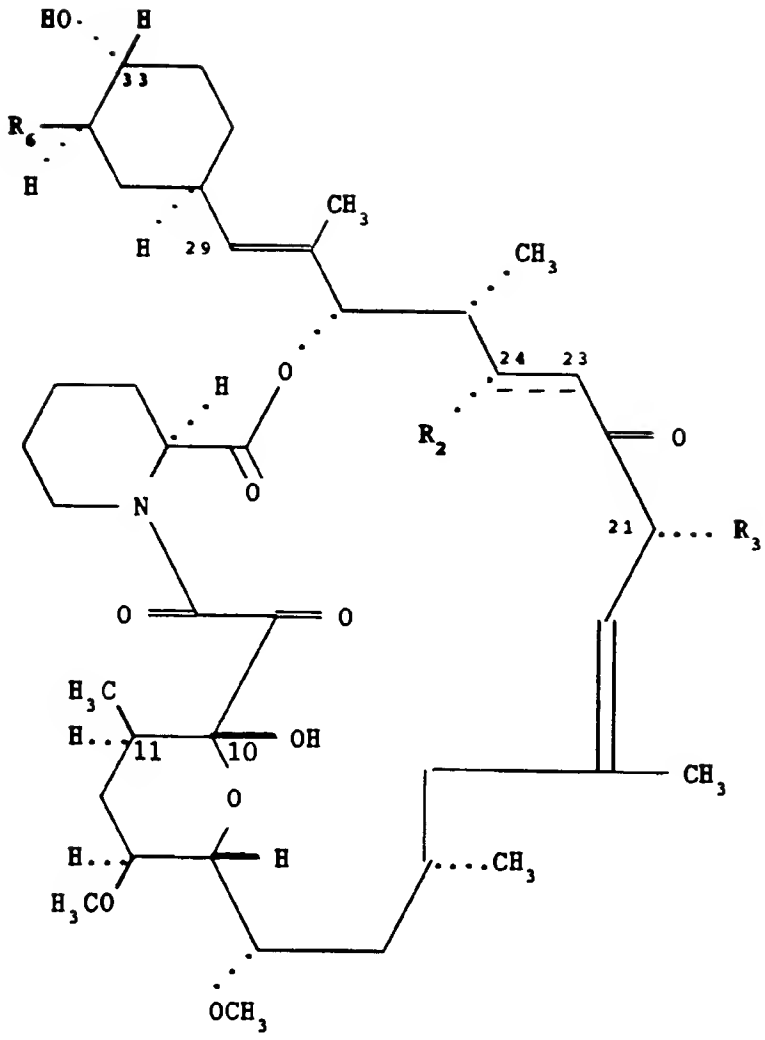
R_1 eine Gruppe (a), wie in Anspruch 1 definiert, ist,

R_2 und R_3 wie in Anspruch 1 definiert sind und

R_4 ein Hydroxyrest ist

(d.h. eine Verbindung Ia),

daß man unter gleichzeitiger Epimerisierung die Hydroxygruppe durch Chlor, Brom, Iod oder einen Azidorest in einer entsprechenden Verbindung mit einem ungeschützten Hydroxyrest in Position 33 ersetzt (d.h. eine Verbindung IIa der Formel IIa

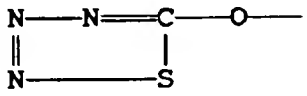


IIa

worin R_2 und R_3 wie oben für Formel I definiert sind und R_6 ein Hydroxy- oder Methoxyrest ist);
b) zur Herstellung einer Verbindung der Formel I, worin

R_1	eine Gruppe (b), wie in Anspruch 1 definiert, ist,
R_2 und R_3	wie in Anspruch 1 definiert sind und
R_4	ein Hydroxyrest ist

(d.h. eine Verbindung Ib),
daß man eine entsprechende Verbindung IIa mit Bromcyan in Gegenwart einer Base behandelt oder eine entsprechende Verbindung IIa mit Thiophosgen versetzt, das entstehende Produkt mit einem anorganischen Azid umsetzt und das entstehende instabile Zwischenprodukt mit einer Gruppe



in Position 33 (d.h. eine Verbindung IIb) sich zu der entsprechenden Verbindung Ib zersetzen läßt;
c) zur Herstellung einer Verbindung der Formel I, worin

R_1	eine Gruppe (d), wie in Anspruch 1 definiert, ist,
R_2 und R_3	wie in Anspruch 1 definiert sind und
R_4	ein Hydroxyrest ist

(d.h. eine Verbindung Ic),
daß man eine entsprechende Verbindung Ib mit einer Säure mit einem nicht-nukleophilen Anion

versetzt, und

- wenn eine entstehende Verbindung der Formel I eine geschützte Hydroxy- und/oder geschützte Aminogruppe hat, gegebenenfalls die Schutzgruppe(n) abspaltet, was eine entsprechende Verbindung der Formel I ergibt mit einer oder mehreren ungeschützten Hydroxy- und/oder ungeschützten Aminogruppen
  (d.h. eine Verbindung Ij),
  wobei dann, wenn R_1 eine Gruppe (a) ist, gleichzeitig ein Wassermolekül abgespalten werden kann und eine Verbindung der Formel I erhalten wird, worin
  R_1 eine Gruppe (a), wie in Anspruch 1 definiert, ist,
  R_2 ein ungeschützter Hydroxyrest ist und in Position 23, 24 eine Einfach- oder Doppelbindung ist; und
  R_4 nicht vorhanden ist und in Position 10, 11 eine Doppelbindung ist
  (d.h. eine Verbindung Ii); oder
- gegebenenfalls eine ungeschützte Hydroxy- und/oder ungeschützte Aminogruppe in einer entstehenden Verbindung der Formel I schützt, was eine entsprechende Verbindung der Formel I ergibt mit einer oder mehreren geschützten Hydroxy- und/oder geschützten Aminogruppen
  (d.h. eine Verbindung Ik),

und die entstehende Verbindung der Formel I in freier Form und, wenn diese Formen existieren, in Salzform gewinnt.

2. Verfahren nach Anspruch 1 zur Herstellung der Verbindung der Formel I, worin R_1 eine Gruppe (d) ist; R_2 ein Hydroxyrest ist und in Position 23, 24 eine Einfachbindung ist; R_3 ein Ethylrest ist; und R_4 ein Hydroxyrest ist und in Position 10, 11 eine Einfachbindung ist; die 29-des-(4-Hydroxy-3-methoxycyclohexyl)-29-(3-formylcyclopentyl)-FR 520 (Verbindung von Beispiel 12) ist.

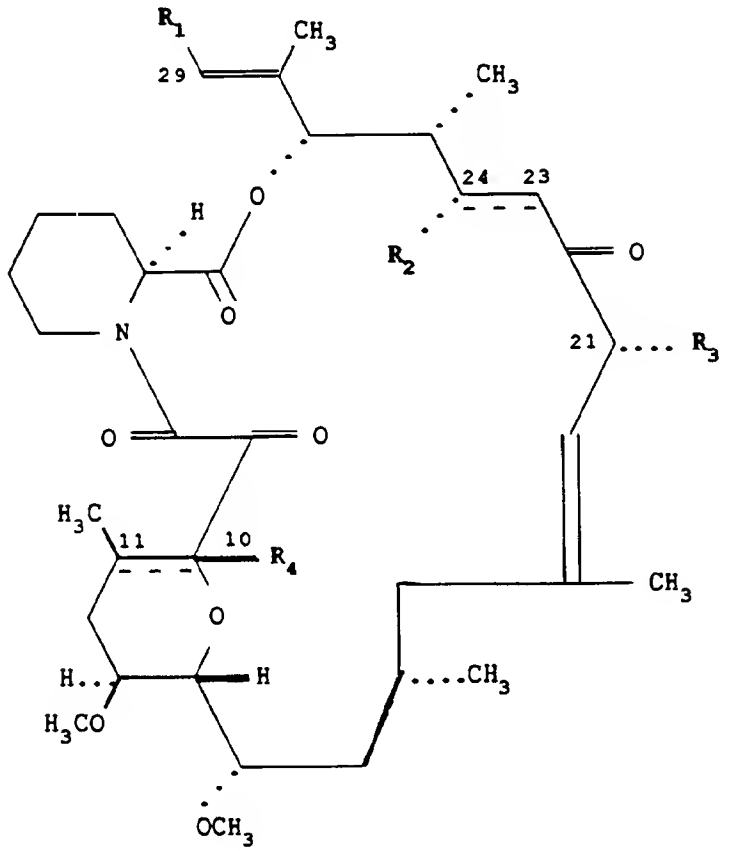
3. Verfahren nach Anspruch 1 zur Herstellung der Verbindung der Formel I, worin R_1 eine Gruppe (a) ist, worin R_5 Chlor ist und R_6 ein Methoxyrest ist; R_2 ein Hydroxyrest ist und in Position 23, 24 eine Einfachbindung ist; R_3 ein Ethylrest ist; und R_4 ein Hydroxyrest ist und in Position 10, 11 eine Einfachbindung ist; die 33-epi-33-Chlor-FR 520 (Verbindung von Beispiel 66a) ist.

4. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, umfassend, daß man eine Verbindung der Formel I, wie in Anspruch 1 definiert, in freier Form oder, wenn diese Formen existieren, in Form des pharmazeutisch annehmbaren Salzes mit einem pharmazeutisch annehmbaren Träger oder Verdünnungsmittel vermischt.

Revendications

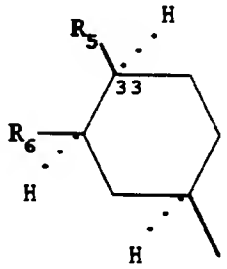
Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Un composé de formule I



I

dans laquelle
soit
R_1 signifie un groupe (a) de formule

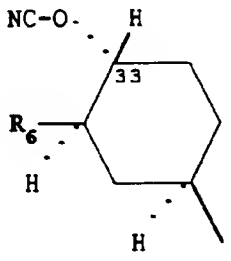


(a)

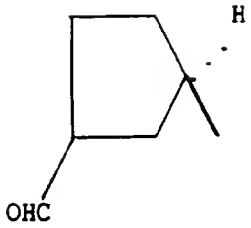
dans laquelle
R_5 signifie le chlore, le brome, l' iode ou un groupe azido, et
R_6 signifie un groupe hydroxy ou méthoxy,
R_2 signifie un groupe oxo et il existe une simple liaison en position 23,24; un groupe hydroxy éventuellement protégé et il existe une simple ou une double liaison en position 23,24; ou il est absent et il existe une double liaison en position 23,24, et
R_4 signifie un groupe hydroxy et il existe une simple liaison en position 10,11; ou il est absent et

il existe une double liaison en position 10,11; ou bien

R_1 signifie un groupe (b) ou (d) de formule



(b) et



(d)

où R_6 est tel que défini plus haut,

R_2 est tel que défini plus haut, et

R_4 signifie un groupe hydroxy et il existe une simple liaison en position 10,11; et

R_3 signifie un groupe méthyle, éthyle, n-propyle ou allyle;

sous forme libre, ou, lorsqu'une telle forme existe, sous forme d'un sel.

2. Un composé selon la revendication 1, qui est un composé **Ip**$_1$, c'est-à-dire un composé de formule I où

R_1 signifie un groupe (a) où R_6 signifie un groupe méthoxy, et

soit

R_5 signifie le chlore ou le brome, et

R_4 signifie un groupe hydroxy et il existe une simple liaison en position 10,11, ou bien

R_5 signifie un groupe azido, et

R_4 signifie un groupe hydroxy et il existe une simple liaison en position 10,11 ou il est absent et il existe une double liaison en position 10,11,

R_2 signifie un groupe hydroxy éventuellement protégé et il existe une simple ou une double liaison en position 23,24, et

R_3 est tel que défini à la revendication 1,

sous forme libre, ou, lorsqu'une telle forme existe, sous forme d'un sel.

3. Un composé selon la revendication 1 qui est un Composé **Ip**$_3$, c'est-à-dire un composé de formule I où

R_1 signifie un groupe (b) où R_6 signifie un groupe méthoxy,

R_2 signifie un groupe hydroxy éventuellement protégé et il existe une simple liaison en position 23,24, ou il est absent et il existe une double liaison en position 23,24,

R_4 signifie un groupe hydroxy et il existe une simple liaison en position 10,11, et

R_3 est tel que défini à la revendication 1,

sous forme libre, ou, lorsqu'une telle forme existe, sous forme d'un sel.

4. Un composé selon la revendication 1 qui est un Composé **Ip**$_4$, c'est-à-dire un composé de formule I où

R_1 signifie un groupe (d),

R_2 signifie un groupe hydroxy éventuellement protégé et il existe une simple liaison en position 23,24 ou il est absent et il existe une double liaison en position 23,24,

R_4 signifie un groupe hydroxy et il existe une simple liaison en position 10,11 et

R_3 est tel que défini à la revendication 1,

sous forme libre, ou, lorsqu'une telle forme existe, sous forme d'un sel.

5. Un Composé de formule I selon la revendication 1, où R_1 signifie un groupe (d); R_2 signifie un groupe hydroxy et il existe une simple liaison en position 23,24; R_3 signifie un groupe éthyle; et R_4 signifie un groupe hydroxy et il existe une simple liaison en position 10,11; qui est le 29-dés-(4-hydroxy-3-méthoxycyclohexyle)-29-(3-formylcyclopentyle)-FR 520 (composé de l'exemple 12).

6. Un composé de formule I selon la revendication 1, où R_1 signifie un groupe (a) où R_5 signifie le chlore et R_6 signifie un groupe méthoxy; R_2 signifie un groupe hydroxy et il existe une simple liaison en position 23,24; R_3 signifie un groupe éthyle; et R_4 signifie un groupe hydroxy et il existe une simple liaison en position 10,11; qui est le 33-épi-33-chloro-FR 520 (composé de l'exemple 66a).

7. Un procédé de préparation d'un composé selon la revendication 1, comprenant

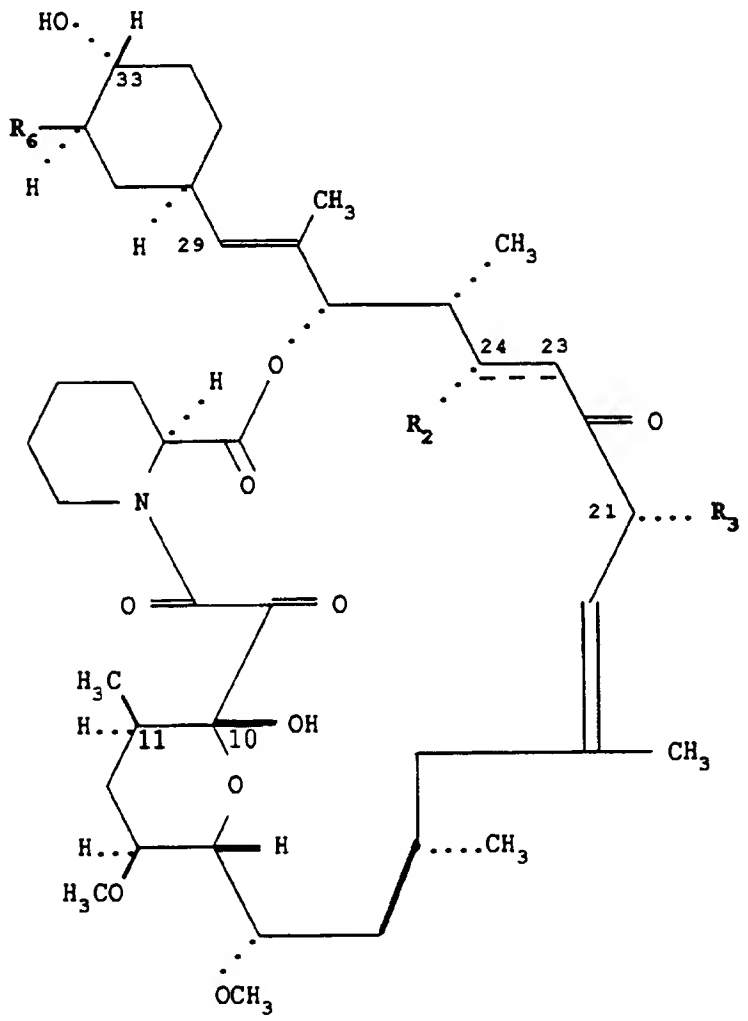
a) pour la préparation d'un composé de formule I où

R_1 signifie un groupe (a) tel que défini à la revendication 1,

R_2 et R_3 sont tels que définis à la revendication 1, et

R_4 signifie un groupe hydroxy (c'est-à-dire **un composé Ia**),

on remplace sous épimérisation simultanée le groupe hydroxy par le chlore, le brome, l'iode ou un groupe azido dans un composé correspondant ayant un groupe hydroxy non protégé en position 33 (c'est-à-dire **un composé IIa,de formule IIa**



IIa

où R_2 et R_3 sont tels que définis à la revendication 1 sous la formule I, et R_6 signifie un groupe hydroxy ou méthoxy);

b) pour la préparation d'un composé de formule I où

R_1 signifie un groupe (b) tel que défini à la revendication 1,

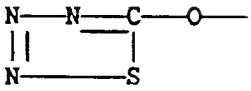
R_2 et R_3 sont tels que définis à la revendication 1, et

R_4 signifie un groupe hydroxy

(c'est-à-dire **un composé Ib**),

on traite un composé correspondant de formule IIa avec du bromure de cyanogène en présence d'une base ou bien

on traite un composé IIa correspondant avec du thiophosgène, on fait réagir le produit résultant avec un azidure minéral et on laisse se décomposer le produit intermédiaire instable résultant ayant un groupe



en position 33 (c'est-à-dire **un composé IIb)**
en un composé Ib correspondant;
c) pour la préparation d'un composé de formule I où
R_1 signifie un groupe (d) tel que défini à la revendication 1,
R_2 et R_3 sont tels que définis à la revendication 1, et
R_4 signifie un groupe hydroxy
(c'est-à-dire **un composé Ic),**
on traite un composé Ib correspondant avec un acide ayant un anion non nucléophile; et

- lorsqu'un composé résultant de formule I comporte un groupe hydroxy protégé et/ou un groupe amino protégé,
  on scinde éventuellement le ou les groupes protecteurs, ce qui donne un composé correspondant de formule I ayant un ou plusieurs groupes hydroxy non protégés et/ou un ou plusieurs groupes amino non protégés, (c'est-à-dire **un composé Ij**), et
  Lorsque R_1 signifie un groupe (a), une molécule d'eau peut être scindée simultanément et on obtient un composé de formule I où
  R_1 signifie un groupe (a) tel que défini à la revendication 1,
  R_2 signifie un groupe hydroxy non protégé et il existe une simple ou une double liaison en position 23,24, et
  R_4 est absent et il existe une double liaison en position 10,11,
  (c'est-à-dire **un composé Ii**); ou bien
- lorsque cela est approprié, on protège éventuellement un groupe hydroxy non protégé et/ou un groupe amino non protégé dans un composé résultant de formule I, ce qui donne un composé correspondant de formule I ayant un ou plusieurs groupes hydroxy protégés et/ou un ou plusieurs groupes amino protégés
  (c'est-à-dire **un composé Ik**);

et on récupère le composé résultant de formule I sous forme libre ou, lorsqu'une telle forme existe, sous forme d'un sel.

8. Une composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 6 sous forme libre ou, lorsqu'une telle forme existe, sous forme d'un sel pharmaceutiquement acceptable, avec un véhicule ou diluant pharmaceutiquement acceptable.

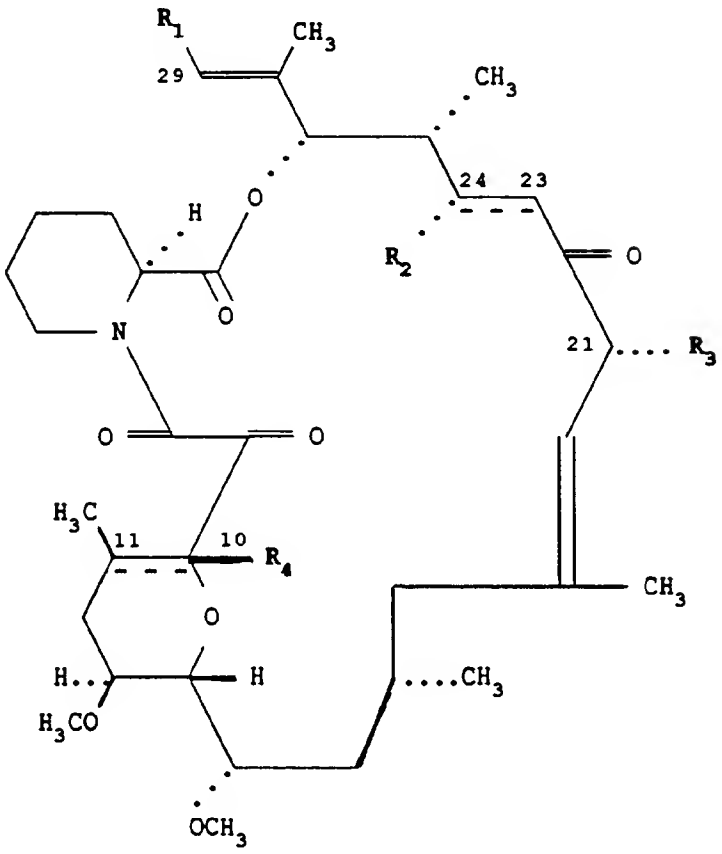
9. Un composé selon l'une quelconque des revendications 1 à 6 sous forme libre ou, lorsqu'une telle forme existe, sous forme d'un sel pharmaceutiquement acceptable, pour l'utilisation comme médicament.

10. Un composé selon la revendication 9, pour une utilisation dans la préparation d'une composition pharmaceutique, par mélange avec un véhicule ou diluant pharmaceutiquement acceptable.

11. Un procédé de préparation d'une composition pharmaceutique comprenant le mélange d'un composé selon l'une quelconque des revendications 1 à 6, sous forme libre ou, lorsqu'une telle forme existe, sous forme d'un sel pharmaceutiquement acceptable, avec un véhicule ou diluant pharmaceutiquement acceptable.

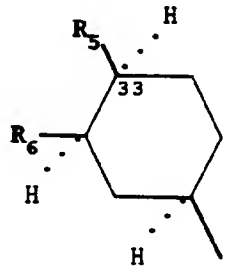
Revendications pour les Etats contractants suivants : ES, GR

1. Un procédé de préparation d'un composé de formule I



I

dans laquelle
soit
R_1 signifie un groupe (a) de formule

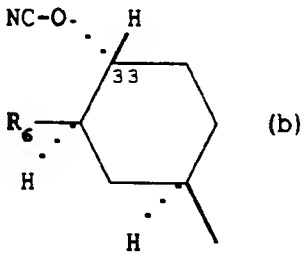


(a)

dans laquelle
R_5 signifie le chlore, le brome, l'iode ou un groupe azido, et
R_6 signifie un groupe hydroxy ou méthoxy,
R_2 signifie un groupe oxo et il existe une simple liaison en position 23,24; un groupe hydroxy éventuellement protégé et il existe une simple ou une double liaison en position 23,24; ou il est absent et il existe une double liaison en position 23,24; et
R_4 signifie un groupe hydroxy et il existe une simple liaison en position 10,11; ou il est absent et

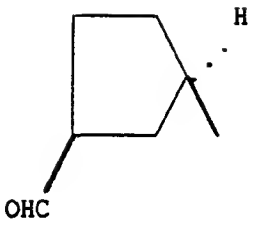
il existe une double liaison en position 10,11; ou bien

R_1 signifie un groupe (b) ou (d) de formule



(b)

et



(d)

où

R_6 est tel que défini plus haut,

R_2 est tel que défini plus haut, et

R_4 signifie un groupe hydroxy et il existe une simple liaison en position 10,11, et

R_3 signifie un groupe méthyle, éthyle, n-propyle ou allyle,

sous forme libre, ou, lorsqu'une telle forme existe, sous forme d'un sel, comprenant

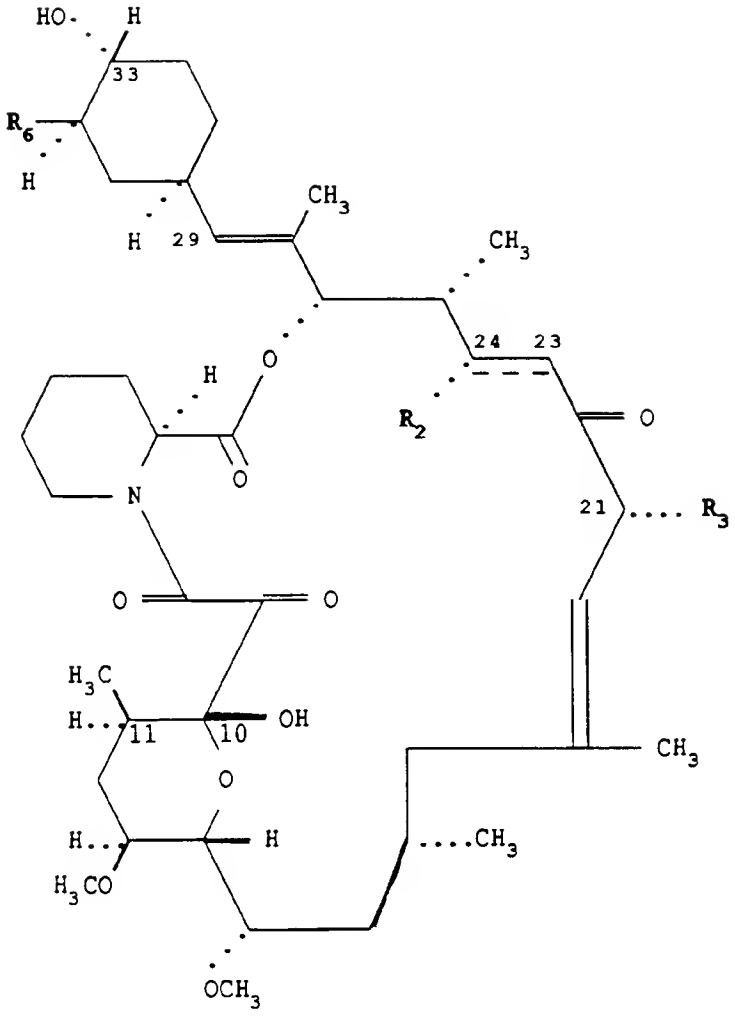
a) pour la préparation d'un composé de formule I où

R_1 signifie un groupe (a) tel que défini à la revendication 1,

R_2 et R_3 sont tels que définis à la revendication 1, et

R_4 signifie un groupe hydroxy (c'est-à-dire **un composé Ia**),

on remplace sous épimérisation simultanée le groupe hydroxy par le chlore, le brome, l'iode ou un groupe azido dans un composé correspondant ayant un groupe hydroxy non protégé en position 33 (c'est-à-dire **un composé IIa, de formule IIa**



IIa

où R_2 et R_3 sont tels que définis plus haut sous la formule I, et R_6 signifie un groupe hydroxy ou méthoxy);

b) pour la préparation d'un composé de formule I où

R_1 signifie un groupe (b) tel que défini à la revendication 1,

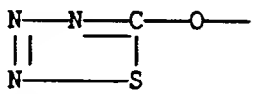
R_2 et R_3 sont tels que définis à la revendication 1, et

R_4 signifie un groupe hydroxy

(c'est-à-dire **un composé Ib**),

on traite un composé correspondant de formule IIa avec du bromure de cyanogène en présence d'une base ou bien

on traite un composé IIa correspondant avec du thiophosgène, on fait réagir le produit résultant avec un azidure minéral et on laisse se décomposer le produit intermédiaire instable résultant ayant un groupe



en position 33 (c'est-à-dire **un composé IIb**) en un composé Ib correspondant;

c) pour la préparation d'un composé de formule I où

R_1 signifie un groupe (d) tel que défini à la revendication 1,

R_2 et R_3 sont tels que définis à la revendication 1, et

R_4 signifie un groupe hydroxy

(c'est-à-dire **un composé Ic**),

on traite un composé Ib correspondant avec un acide ayant un anion non nucléophile, et

- lorsqu'un composé résultant de formule I comporte un groupe hydroxy protégé et/ou un groupe amino protégé,
  on scinde éventuellement le ou les groupes protecteurs, ce qui donne un composé correspondant de formule I ayant un ou plusieurs groupes hydroxy non protégés et/ou un ou plusieurs groupes amino non protégés, (c'est-à-dire **un composé Ij**), et
  Lorsque R_1 signifie un groupe (a), une molécule d'eau peut être scindée simultanément et on obtient un composé de formule I où
  R_1 signifie un groupe (a) tel que défini à la revendication 1,
  R_2 signifie un groupe hydroxy non protégé et il existe une simple ou une double liaison en position 23,24, et
  R_4 est absent et il existe une double liaison en position 10,11,
  (c'est-à-dire **un composé Ii**), ou bien
- lorsque cela est approprié, on protège éventuellement un groupe hydroxy non protégé et/ou un groupe amino non protégé dans un composé de formule I résultant, ce qui donne un composé correspondant de formule I ayant un ou plusieurs groupes hydroxy protégés et/ou un ou plusieurs groupes amino protégés

(c'est-à-dire **un composé Ik**),

et on récupère le composé résultant de formule I sous forme libre ou, lorsqu'une telle forme existe, sous forme d'un sel.

2. Un procédé selon la revendication 1 pour la préparation du composé de formule I, où R_1 signifie un groupe (d); R_2 signifie un groupe hydroxy et il existe une simple liaison en position 23,24; R_3 signifie un groupe éthyle; et R_4 signifie un groupe hydroxy et il existe une simple liaison en position 10,11; qui est le 29-dés-(4-hydroxy-3-méthoxycyclohexyle)-29-(3-formylcyclo-pentyle)-FR 520(composé de l'exemple 12).

3. Un procédé selon la revendication 1 pour la préparation du composé de formule I, où R_1 signifie un groupe (a) où R_5 signifie le chlore et R_6 signifie un groupe méthoxy; R_2 signifie un groupe hydroxy et il existe une simple liaison en position 23,24; R_3 signifie un groupe éthyle; et R_4 signifie un groupe hydroxy et il existe une simple liaison en position 10,11; qui est le 33-épi-33-chloro-FR 520 (composé de l'exemple 66a).

4. Un procédé de préparation d'une composition pharmaceutique comprenant le mélange d'un composé de formule I tel que défini à la revendication 1 sous forme libre ou, lorsqu'une telle forme existe, sous forme d'un sel pharmaceutiquement acceptable, avec un véhicule ou diluant pharmaceutiquement acceptable.